INVENTOR SEARCH

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=> fil agricola pascal caba biotechno wpix biosis dissabs esbio embase scisearch
FILE 'AGRICOLA' ENTERED AT 11:02:14 ON 18 JUN 2010

FILE 'PASCAL' ENTERED AT 11:02:14 ON 18 JUN 2010
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FILE 'CABA' ENTERED AT 11:02:14 ON 18 JUN 2010
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FILE 'BIOTECHNO' ENTERED AT 11:02:14 ON 18 JUN 2010
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FILE 'WPIX' ENTERED AT 11:02:14 ON 18 JUN 2010
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FILE 'BIOSIS' ENTERED AT 11:02:14 ON 18 JUN 2010
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FILE 'DISSABS' ENTERED AT 11:02:14 ON 18 JUN 2010
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FILE 'ESBIOBASE' ENTERED AT 11:02:14 ON 18 JUN 2010
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FILE 'EMBASE' ENTERED AT 11:02:14 ON 18 JUN 2010
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FILE 'SCISEARCH' ENTERED AT 11:02:14 ON 18 JUN 2010
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=> d que l126

L91          60 SEA ZANKEL T?/AU
L92         797 SEA STARR C?/AU
L126          2 SEA (L91 OR L92) AND (L94 OR (L93 AND L96)) AND (L97 OR L98 OR
                L99 OR L100 OR L101 OR L102 OR L103 OR L104 OR L105 OR L106 OR
                L107 OR L108 OR L109 OR L110 OR L111 OR L112 OR L113 OR L114
                OR L115 OR L116 OR L117 OR L118 OR L119 OR L120 OR L121 OR
                L122 OR L123 OR L124 OR L125)


=> fil hcapl; d que l29

FILE 'HCAPLUS' ENTERED AT 11:02:16 ON 18 JUN 2010
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FILE COVERS 1907 - 18 Jun 2010  VOL 152 ISS 26
FILE LAST UPDATED: 17 Jun 2010  (20100617/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Apr 2010
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Apr 2010

HCAplus now includes complete International Patent Classification (IPC)
reclassification data for the second quarter of 2010.

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy.html

This file contains CAS Registry Numbers for easy and accurate
substance identification.
'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE


L7          189 SEA FILE=REGISTRY SPE=ON  ABB=ON  GALACTOSIDASE, A?/CN
L8            2 SEA FILE=HCAPLUS SPE=ON  ABB=ON  US2007-588425/APPS
L9         4266 SEA FILE=HCAPLUS SPE=ON  ABB=ON  L7
L10        3364 SEA FILE=HCAPLUS SPE=ON  ABB=ON  GALACTOSIDASE/OBI(L)A/OB
                I
L13      212052 SEA FILE=HCAPLUS SPE=ON  ABB=ON  RECOMB?/OBI
L14     1993781 SEA FILE=HCAPLUS SPE=ON  ABB=ON  HUMAN/OBI
L15         105 SEA FILE=HCAPLUS SPE=ON  ABB=ON  L9(L)L13
L16         141 SEA FILE=HCAPLUS SPE=ON  ABB=ON  L10(L)L13
L17          34 SEA FILE=HCAPLUS SPE=ON  ABB=ON  L10(L)L13(L)L14
L18          31 SEA FILE=HCAPLUS SPE=ON  ABB=ON  GGA/OBI(L)(L13 OR L14)
L24          21 SEA FILE=HCAPLUS SPE=ON  ABB=ON  ZANKEL T?/AU
L25         189 SEA FILE=HCAPLUS SPE=ON  ABB=ON  STARR C?/AU
L29           2 SEA FILE=HCAPLUS SPE=ON  ABB=ON  L8 OR ((L24 OR L25) AND (L15
                OR L16 OR L17 OR L18))


=> fil medl; d que l64

FILE 'MEDLINE' ENTERED AT 11:02:17 ON 18 JUN 2010

 FILE LAST UPDATED: 17 Jun 2010 (20100617/UP).  FILE COVERS 1947 TO DATE.

 MEDLINE and LMEDLINE have been updated with the 2010 Medical Subject
 Headings (MeSH) vocabulary and tree numbers from the U.S.  National Library
 of Medicine (NLM).  Additional information is available at

 http://www.nlm.nih.gov/pubs/techbull/nd09/nd09_medline_data_changes_2010.html.

 The Medline file has been reloaded effective January 24, 2010.  See HELP
 RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

 See HELP RANGE before carrying out any RANGE search.


L56          10 SEA FILE=MEDLINE SPE=ON  ABB=ON  ZANKEL T?/AU
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L57          116 SEA FILE=MEDLINE SPE=ON  ABB=ON  STARR C?/AU
L58            2 SEA FILE=MEDLINE SPE=ON  ABB=ON  L56 AND L57
L59         3349 SEA FILE=MEDLINE SPE=ON  ABB=ON  ALPHA-GLUCOSIDASES/CT
L60           35 SEA FILE=MEDLINE SPE=ON  ABB=ON  RHGAA OR RH GAA
L62        17870 SEA FILE=MEDLINE SPE=ON  ABB=ON  LYSOSOMAL STORAGE DISEASES+NT/
                 CT
L63            0 SEA FILE=MEDLINE SPE=ON  ABB=ON  (L56 OR L57) AND (L60 OR (L59
                 AND L62))
L64            2 SEA FILE=MEDLINE SPE=ON  ABB=ON  (L58 OR L63)


=> dup rem l64,l29,l126

FILE 'MEDLINE' ENTERED AT 11:02:18 ON 18 JUN 2010

FILE 'HCAPLUS' ENTERED AT 11:02:18 ON 18 JUN 2010
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2010 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'WPIX' ENTERED AT 11:02:18 ON 18 JUN 2010
COPYRIGHT (C) 2010 THOMSON REUTERS
PROCESSING COMPLETED FOR L64
PROCESSING COMPLETED FOR L29
PROCESSING COMPLETED FOR L126
L147           5 DUP REM L64 L29 L126 (1 DUPLICATE REMOVED)
                 ANSWERS '1-2' FROM FILE MEDLINE
                 ANSWERS '3-4' FROM FILE HCAPLUS
                 ANSWER '5' FROM FILE WPIX

=> d iall 1-2; d ibib ab hitind 3-4; d ifull 5

L147 ANSWER 1 OF 5     MEDLINE on STN
ACCESSION NUMBER:    2004415058     MEDLINE  Full-text
DOCUMENT NUMBER:     PubMed ID: 15170390
TITLE:               Lipoprotein receptor binding, cellular uptake, and
                     lysosomal delivery of fusions between the
                     receptor-associated protein (RAP) and alpha-L-iduronidase
                     or acid alpha-glucosidase.
AUTHOR:              Prince William S; McCormick Lynn M; Wendt Dan J;
                     Fitzpatrick Paul A; Schwartz Keri L; Aguilera Allora I;
                     Koppaka Vishwanath; Christianson Terri M; Vellard Michel C;
                     Pavloff Nadine; Lemontt Jeff F; Qin Minmin; Starr
                     Chris M; Bu Guojun; Zankel Todd C
CORPORATE SOURCE:    BioMarin Pharmaceutical, Inc., Novato, CA 94949, USA.
SOURCE:              The Journal of biological chemistry, (2004 Aug 13) Vol.
                     279, No. 33, pp. 35037-46.  Electronic Publication:
                     2004-05-31.
                     Journal code: 2985121R. ISSN: 0021-9258. L-ISSN: 0021-9258.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
                     (RESEARCH SUPPORT, NON-U.S. GOV'T)
                     (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200409
ENTRY DATE:          Entered STN: 24 Aug 2004
                     Last Updated on STN: 25 Sep 2004
                     Entered Medline: 24 Sep 2004
ABSTRACT:
```

Enzyme replacement therapy for lysosomal storage disorders depends on efficient uptake of recombinant enzyme into the tissues of patients. This uptake is mediated by oligosaccharide receptors including the cation-independent mannose 6-phosphate receptor and the mannose receptor. We have sought to exploit alternative receptor systems that are independent of glycosylation but allow for efficient delivery to the lysosome. Fusions of the human lysosomal enzymes alpha-l-iduronidase or acid alpha-glucosidase with the receptor-associated protein were efficiently endocytosed by lysosomal storage disorder patient fibroblasts, rat C6 glioma cells, mouse C2C12 myoblasts, and recombinant Chinese hamster ovary cells expressing individual members of the low-density lipoprotein receptor family. Uptake of the fusions exceeded that of phosphorylated enzyme in all cases, often by an order of magnitude or greater. Uptake was specifically mediated by members of the low-density lipoprotein receptor protein family and was followed by delivery of the fusions to the lysosome. The advantages of the lipoprotein receptor system over oligosaccharide receptor systems include more efficient cellular delivery and the potential for transcytosis of ligands across tight endothelia, including the blood-brain barrier.

CONTROLLED TERM: Animals
Blotting, Western
CHO Cells
Carbohydrates: CH, chemistry
Cell Line, Tumor
Cricetinae
Dose-Response Relationship, Drug
Electrophoresis
Endocytosis
Fibroblasts: ME, metabolism
Glioma: ME, metabolism
Glycosaminoglycans: CH, chemistry
Humans
*Iduronidase: ME, metabolism
Kinetics
Ligands
Lipoproteins, LDL: ME, metabolism
*Lysosomes: ME, metabolism
Mice
Oligosaccharides: CH, chemistry
Phosphorylation
Plasmids: ME, metabolism
Protein Binding
Rats
*Receptors, Lipoprotein: ME, metabolism
Recombinant Fusion Proteins: ME, metabolism
Recombinant Proteins: ME, metabolism
Time Factors
*alpha-Glucosidases: ME, metabolism

CHEMICAL NAME: 0 (Carbohydrates); 0 (Glycosaminoglycans); 0 (Ligands); 0 (Lipoproteins, LDL); 0 (Oligosaccharides); 0 (Receptors, Lipoprotein); 0 (Recombinant Fusion Proteins); 0 (Recombinant Proteins); EC 3.2.1.20 (alpha-Glucosidases); EC 3.2.1.76 (Iduronidase)

L147 ANSWER 2 OF 5 MEDLINE on STN
ACCESSION NUMBER: 2004413009 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 15175008
TITLE: Overexpression of inactive arylsulphatase mutants and in vitro activation by light-dependent oxidation with vanadate.
AUTHOR: Christianson Terri M; Starr Chris M; Zankel

Todd C

CORPORATE SOURCE: BioMarin Pharmaceutical Inc., 371 Bel Marin Keys Blvd., Novato, CA 94949, USA.
SOURCE: The Biochemical journal, (2004 Sep 1) Vol. 382, No. Pt 2, pp. 581-7.
Journal code: 2984726R. E-ISSN: 1470-8728. L-ISSN: 0264-6021.
Report No.: NLM-PMC1133815.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200502
ENTRY DATE: Entered STN: 20 Aug 2004
Last Updated on STN: 23 Feb 2005
Entered Medline: 22 Feb 2005

ABSTRACT:
Arylsulphatases B (ASB) and A (ASA) are subject to a unique post-translational modification that is required for their function. The modification reaction, conversion of an active-site cysteine into a formylglycine, becomes saturated when these enzymes are overexpressed. We have removed the possibility of in vivo modification by expressing mutants of ASB and ASA in which the active-site cysteine is substituted with a serine. These mutants are expressed much more efficiently when compared with the native enzymes under identical conditions. The purified ASB mutant can then be converted into catalytically active ASB in vitro using vanadate and light.

CONTROLLED TERM: Animals
*Arylsulfatases: BI, biosynthesis
Arylsulfatases: GE, genetics
*Arylsulfatases: ME, metabolism
Arylsulfatases: SE, secretion
CHO Cells: CH, chemistry
CHO Cells: ME, metabolism
CHO Cells: SE, secretion
Cell Line
Cricetinae
DNA, Complementary: GE, genetics
Enzyme Activation
Humans
*Light
Liver: EN, enzymology
*Mutation, Missense
Mutation, Missense: GE, genetics
Oxidation-Reduction
Transfection: MT, methods
Vanadates: CH, chemistry
*Vanadates: ME, metabolism

CHEMICAL NAME: 0 (DNA, Complementary); 0 (Vanadates); EC 3.1.6.1 (Arylsulfatases)

L147 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2010 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2005:902745 HCAPLUS Full-text
DOCUMENT NUMBER: 143:246879
TITLE: Manufacture of highly phosphorylated lysosomal enzymes and uses thereof
INVENTOR(S): Zankel, Todd; Kakkis, Emil D.
PATENT ASSIGNEE(S): Biomarin Pharmaceutical Inc., USA

```
SOURCE:                  PCT Int. Appl., 72 pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  2
PATENT INFORMATION:

     PATENT NO.          KIND   DATE       APPLICATION NO.        DATE
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     WO 2005077093        A2    20050825   WO 2005-US4345         20050207
     WO 2005077093        A3    20051215
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, SM
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
             EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
             RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
             MR, NE, SN, TD, TG
     AU 2005211775        A1    20050825   AU 2005-211775         20050207
     AU 2005211775        B2    20091008
     CA 2556245           A1    20050825   CA 2005-2556245        20050207
     EP 1720405           A2    20061115   EP 2005-722947         20050207
         R:  AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
             IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR
     BR 2005007440        A     20070710   BR 2005-7440           20050207
     JP 2007523648        T     20070823   JP 2006-552376         20050207
     US 20080014188       A1    20080117   US 2007-588425         20070606 <--
     US 20090191178       A1    20090730   US 2008-182818         20080730 <--
PRIORITY APPLN. INFO.:                     US 2004-542586P     P  20040206
                                           WO 2005-US4345      W  20050207
                                           US 2007-588425      A2 20070606 <--
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB    This invention provides compns. of highly phosphorylated lysosomal enzymes,
      their pharmaceutical compns., methods of producing and purifying such compds.
      and compns. and their use in the diagnosis, prophylaxis, or treatment of
      diseases and conditions, including particularly lysosomal storage diseases.
IC    ICM  C12P
CC    16-6 (Fermentation and Bioindustrial Chemistry)
      Section cross-reference(s): 1
OS.CITING REF COUNT:     2      THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD
                                (2 CITINGS)
REFERENCE COUNT:         6      THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L147 ANSWER 4 OF 5  HCAPLUS  COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER:        2009:919105  HCAPLUS  Full-text
DOCUMENT NUMBER:         151:213339
TITLE:                   Manufacture of recombinant human acid
                         alpha-glucosidase and uses thereof for the treatment
                         of lysosomal storage diseases
INVENTOR(S):             Zankel, Todd C.; Starr, Christopher
                         M.
PATENT ASSIGNEE(S):      BioMarin Pharmaceutical Inc., USA
SOURCE:                  U.S. Pat. Appl. Publ., 66pp., Cont.-in-part of U.S.
                         Ser. No. 588,425.
                         CODEN: USXXCO
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DOCUMENT TYPE:          Patent
LANGUAGE:               English
FAMILY ACC. NUM. COUNT:  2
PATENT INFORMATION:

     PATENT NO.          KIND   DATE       APPLICATION NO.        DATE
     ---------------     ----   --------   --------------------   --------
     US 20090191178       A1    20090730   US 2008-182818         20080730 <--
     WO 2005077093        A2    20050825   WO 2005-US4345         20050207
     WO 2005077093        A3    20051215
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, SM
        RW:  BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
             EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
             RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
             MR, NE, SN, TD, TG
     US 20080014188       A1    20080117   US 2007-588425         20070606 <--
PRIORITY APPLN. INFO.:                     US 2004-542586P     P  20040206
                                           WO 2005-US4345      W  20050207
                                           US 2007-588425      A2 20070606 <--
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB    This invention provides compns. of highly phosphorylated lysosomal enzymes, in
      particular, a recombinant human acid alpha-glucosidase (rhGAA) enzyme, their
      pharmaceutical compns., methods of producing and purifying such lysosomal
      enzymes and compns. and their use in the diagnosis, prophylaxis, or treatment
      of diseases and conditions, including particularly lysosomal storage diseases.
INCL 424094610; 435200000; 435069100; 435358000
CC    3-2 (Biochemical Genetics)
      Section cross-reference(s): 1, 7, 63
IT    1174598-21-0P, Galactosidase, α- (
      human gene GAA)   1174598-22-1P   1174598-23-2P
      1174598-24-3P   1174598-25-4P
      RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified);
      PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use);
      BIOL (Biological study); PREP (Preparation); USES (Uses)
         (amino acid sequence; manufacture of recombinant human
         acid alpha-glucosidase and uses thereof for treatment of
         lysosomal storage diseases)
IT    9025-35-8P
      RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified);
      PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use);
      BIOL (Biological study); PREP (Preparation); USES (Uses)
         (gene GAA, of human, recombinant; manufacture of
         recombinant human acid alpha-glucosidase and uses thereof for
         treatment of lysosomal storage diseases)


L147 ANSWER 5 OF 5  WPIX COPYRIGHT 2010       THOMSON REUTERS on STN
ACCESSION NUMBER:      2005-091652 [200510]   WPIX
DOC. NO. CPI:          C2005-030912 [200510]
TITLE:                 Compound useful for treating Alzheimer's disease and
                       Parkinson's disease, comprises megalin-binding moiety
                       conjugated to agent of interest
```

DERWENT CLASS: B04; B05; D16
INVENTOR: GABATHULER R; STARR C M; ZANKEL T; STARR C
PATENT ASSIGNEE: (BIOM-N) BIOMARIN PHARM; (BIOM-N) BIOMARIN PHARM INC; (STAR-I) STARR C M; (ZANK-I) ZANKEL T; (RAPT-N) RAPTOR PHARM INC
COUNTRY COUNT: 107

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2005002515	A2	20050113	(200510)*	EN	192[25]	
US 20050026823	A1	20050203	(200511)	EN		
US 20050042227	A1	20050224	(200515)	EN		
AU 2004253471	A1	20050113	(200604)	EN		
US 20060029609	A1	20060209	(200612)	EN		
EP 1638605	A2	20060329	(200623)	EN		
AU 2004253471	A2	20050113	(200654)	EN		
JP 2007526227	W	20070913	(200762)	JA	93	
US 7560431	B2	20090714	(200946)	EN		
US 7569544	B2	20090804	(200951)	EN		
US 20100028370	A1	20100204	(201011)	EN		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005002515	A2	WO 2004-US19153	20040617
US 20050026823	A1	US 2003-600862	20030620
US 20050042227	A1 CIP of	US 2003-600862	20030620
US 20060029609	A1 Div Ex	US 2003-600862	20030620
US 7560431	B2 Div Ex	US 2003-600862	20030620
US 7569544	B2 CIP of	US 2003-600862	20030620
US 20050042227	A1	US 2004-812849	20040330
US 7569544	B2	US 2004-812849	20040330
AU 2004253471	A1	AU 2004-253471	20040617
AU 2004253471	A2	AU 2004-253471	20040617
EP 1638605	A2	EP 2004-776636	20040617
EP 1638605	A2	WO 2004-US19153	20040617
JP 2007526227	W	WO 2004-US19153	20040617
US 20060029609	A1	US 2005-202566	20050812
US 7560431	B2	US 2005-202566	20050812
JP 2007526227	W	JP 2006-517307	20040617
US 20100028370	A1 CIP of	US 2003-600862	20030620
US 20100028370	A1 Cont of	US 2004-812849	20040330
US 20100028370	A1	US 2009-508956	20090724

FILING DETAILS:

PATENT NO	KIND		PATENT NO	
AU 2004253471	A1	Based on	WO 2005002515	A
EP 1638605	A2	Based on	WO 2005002515	A
AU 2004253471	A2	Based on	WO 2005002515	A
JP 2007526227	W	Based on	WO 2005002515	A
US 20100028370	A1	Cont of	US 7569544	B

PRIORITY APPLN. INFO: US 2004-812849 20040330
US 2003-600862 20030620

US 2005-202566 20050812
US 2009-508956 20090724

INT. PATENT CLASSIF.:
MAIN: A61K039-395
IPC ORIGINAL: A61K0031-519 [I,C]; A61K0031-52 [I,A]; A61K0038-00 [I,A]; A61K0038-00 [I,C]; A61K0038-18 [I,A]; A61K0038-18 [I,C]; A61K0038-43 [I,A]; A61K0038-43 [I,C]; A61K0039-395 [I,C]; A61K0039-395 [I,A]; A61K0039-395 [I,C]; A61K0047-48 [I,A] ; A61K0047-48 [I,C]; A61K0047-48 [I,A]; A61K0047-48 [I,C] ; A61K0049-00 [I,A]; A61K0049-00 [I,C]; A61P0021-00 [I,C] ; A61P0021-02 [I,A]; A61P0025-00 [I,C]; A61P0025-00 [I,A] ; A61P0025-00 [I,C]; A61P0025-16 [I,A]; A61P0025-28 [I,A] ; A61P0035-00 [I,A]; A61P0035-00 [I,C]; A61P0043-00 [I,A] ; A61P0043-00 [I,C]; C07K0014-435 [I,C]; C07K0014-435 [I,A]; C07K0014-435 [I,C]; C07K0014-47 [I,A]; C07K0014-48 [I,A]; C07K0014-485 [I,A]; C07K0014-50 [I,A]; C07K0014-62 [I,A]; C07K0014-705 [I,A]; C07K0014-76 [I,A]; C07K0014-775 [I,A]; C07K0016-00 [I,A]; C07K0016-00 [I,C]; C07K0016-46 [I,A]; C07K0016-46 [I,C]; C07K0019-00 [I,A]; C07K0019-00 [I,C]; C12N0015-09 [I,A]; C12N0015-09 [I,C]; C12N0009-02 [I,A]; C12N0009-02 [I,C]; C12N0009-24 [I,A]; C12N0009-24 [I,C]; C12N0009-26 [I,A]; C12N0009-26 [I,C]
IPC RECLASSIF.: A61K [I,S]; A61K0038-17 [I,A]; A61K0038-17 [I,C]; A61K0039-395 [I,A]; A61K0039-395 [I,C]; A61K0048-00 [I,A] ; A61K0048-00 [I,C]; C07K0014-435 [I,C]; C07K0014-705 [I,A]
ECLA: A61K0047-48R6; A61K0049-00
ICO: Y01N0002:00
USCLASS NCLM: 424/178.100; 424/181.100; 514/012.000
NCLS: 424/009.100; 424/179.100; 514/012.000; 514/044.000; 530/350.000; 530/391.100; 530/391.500; 530/391.900
JAP. PATENT CLASSIF.:
MAIN/SEC.: A61K0031-52; A61K0037-02; A61K0037-48; A61K0047-48; A61P0021-02; A61P0025-00; A61P0025-16; A61P0025-28; A61P0035-00; A61P0043-00 111; C07K0014-47 (ZNA); C07K0014-485; C07K0014-62; C07K0014-705; C07K0014-76; C07K0014-775; C07K0019-00; C12N0015-00 A; C12N0009-02; C12N0009-24; C12N0009-26 A
FTERM CLASSIF.: 4B024; 4B050; 4C076; 4C084; 4C086; 4C201; 4H045; 4B024/AA01; 4C086/AA01; 4C084/AA02; 4C086/AA02; 4C084/AA07; 4H045/AA10; 4H045/AA30; 4H045/BA09; 4C084/BA41; 4H045/BA41; 4C084/BA44; 4H045/BA54; 4B024/CA02; 4B024/CA11; 4H045/CA40; 4C084/CA53; 4C084/CA59; 4C086/CB07; 4B050/CC03; 4B050/CC05; 4B050/CC07; 4C076/CC29; 4C076/CC41; 4B024/DA02; 4C084/DA11; 4H045/DA70; 4H045/DA76; 4H045/DA89; 4C084/DC01; 4B050/DD11; 4H045/EA21; 4C076/EE59; 4H045/FA74; 4C076/FF70; 4B024/GA11; 4B024/HA08; 4B024/HA17; 4B050/LL01; 4C084/MA02; 4C086/MA02; 4C086/MA04; 4C086/MA07; 4C084/NA05; 4C086/NA05; 4C084/NA13; 4C084/ZA02; 4C086/ZA02; 4C086/ZA16; 4C084/ZA16.1; 4C086/ZA22; 4C084/ZA22.1; 4C086/ZA94; 4C084/ZA94.1; 4C086/ZB08; 4C084/ZB08.2; 4C086/ZB26; 4C084/ZB26.1; 4C084/ZC19.2; 4C086/ZC75; 4C084/ZC75.2

BASIC ABSTRACT:
WO 2005002515 A2 UPAB: 20090723
NOVELTY - A compound (I) comprises a megalin-binding moiety conjugated to an agent of interest.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a chimeric molecule (II) for (a) transcytotic delivery into the brain across the blood-brain barrier, comprising a megalin ligand conjugated to an active agent to be delivered across the blood-brain barrier by transcytosis, where the megalin ligand facilitates transport of the chimeric molecule across the blood-brain barrier, or (b) delivery into the brain by transcytosis across the blood-brain barrier, comprising lipoprotein receptor-related protein (LRP) ligand conjugated to an active agent to be delivered across the blood-brain barrier by transcytosis, where the LRP ligand binds preferentially to megalin as compared to LRP1; (2) a pharmaceutical composition (PC1) comprising (I) or (II) in a carrier, diluent or excipient;
(3) delivering an agent into the central nervous system (CNS) of an animal, involves administering the animal the agent conjugated to a megalin-binding moiety, where the transport of the agent conjugated to megalin-binding moiety across the blood-brain barrier of the animal is greater than the transport of the agent in the absence of conjugation to the megalin-binding moiety;
(4) increasing transcytosis of an agent, involving conjugating the agent to a megalin-binding moiety, where transcytosis of the agent when conjugated to the megalin-binding moiety is greater than transcytosis of the agent in the absence of the conjugation; (5) treating (M1) a disorder in a mammal involving administering to the animal a therapeutic agent conjugated to a megalin-binding moiety; (6) delivering a therapeutic enzyme to a lysosomal compartment in a cell expressing megalin, involving contacting the cell with a composition comprising the therapeutic enzyme conjugated to a megalin-binding moiety, where the uptake of the therapeutic enzyme into the lysosomal compartment of the cell is mediated through megalin present on the surface of the cell; and (7) delivering a therapeutic enzyme to a lysosome in a cell of a subject, involving administering to the subject a compound comprising receptor associated protein (RAP) or RAP polypeptide conjugated to a therapeutic or diagnostic agent, transporting the compound across the cell membrane, contacting the compound with an LRP receptor on the cell, facilitating entry of the compound into the cell, and delivering the compound to the lysosome in the cell. ACTIVITY - Antiparkinsonian; Neuroprotective; Nootropic; Cytostatic; Nephrotropic; Cardiovascular-Gen.; CNS-Gen.; Antilipemic.
MECHANISM OF ACTION - Decreases amount of storage granules in brain tissue or meningeal tissue; Reduces amount of glycosaminoglycan in brain cell; Reduces high pressure hydrocephalus; Reduces spinal cord compression; Reduces number and/or size of perivascular cysts around brain vessels (claimed). In vivo analysis of a composition comprising therapeutic enzyme (alpha-L-iduronidase) linked to receptor associated protein (RAP) in reducing glycosaminoglycan (GAG) was carried out as follows. A composition comprising the alpha-L-iduronidase) linked to RAP was administered intravenously into the patients having mucopolysaccharidosis type I (MPS-I) disorder. Efficacy of the composition was determined by measuring the percentage reduction in urinary GAG excretion overtime. The urinary GAG levels in MPS-I patients was compared with the levels in untreated MPS-I patients. The result indicated greater than 50% reduction in excretion of undegraded GAGs in the MPS-I patients, following the treatment.
USE - (I) or (M1) is useful for treating a disorder in a mammal, where the disorder is a disorder of CNS, and the disorder is chosen from Alzheimer's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis and CNS cancer. The disorder is CNS cancer and the agent is a cancer chemotherapeutic agent. (I) or PC1 is useful for treating a lysosomal storage disease (LSD) in a subject, which involves administering to the subject PC1 comprising a megalin-binding moiety conjugated to a therapeutic agent used in the treatment of the LSD, to ameliorate the symptoms of the LSD, which is chosen from aspartylglucosaminuria, cholesterol ester storage disease, Wolman disease, cystinosis, Danon disease, Fabry disease, Farber lipogranulomatosis, Farber disease, fucosidosis, galactosialidosis types I/II, Gaucher disease types I/II/III, Gaucher disease, globoid cell leukodystrophy, Krabbe disease, glycogen storage disease II, Pompe disease, GM1-gangliosidosis types I/II/III,

GM2-gangliosidosis type I, Tay- Sachs disease, GM2-gangliosidosis type II, Sandhoff disease, GM2-gangliosidosis, alpha-mannosidosis types I/II, beta-mannosidosis, metachromatic leukodystrophy, mucolipidosis type I, sialidosis types I/II, mucolipidosis types II/III, I-cell disease, mucolipidosis type IIIC, pseudo-Hurler polydystrophy, mucopolysaccharidosis type I, mucopolysaccharidosis type II, Hunter syndrome, mucopolysaccharidosis type IIIA, Sanfilippo syndrome, mucopolysaccharidosis type IIIB, mucopolysaccharidosis type IIIC, mucopolysaccharidosis type IIID, mucopolysaccharidosis type IVA, Morquio syndrome, mucopolysaccharidosis type IVB, mucopolysaccharidosis type VI, mucopolysaccharidosis type VII, Sly syndrome, mucopolysaccharidosis type IX, multiple sulfatase deficiency, neuronal ceroid lipofuscinosis, CLN1 Batten disease, Niemann-Pick disease types A/B, Niemann-Pick disease, Niemann-Pick disease type C1, Niemann-Pick disease type C2, pycnodysostosis, Schindler disease types I/II, Schindler disease and sialic acid storage disease (all claimed). (I) is useful in the diagnosis of a variety of CNS and non-CNS diseases, conditions and disorders, including cancer and LSD.

ADVANTAGE - The megalin ligand moiety is an excellent vehicle for enhanced delivery of chemotherapeutic agents to brain tumors and other neoplasia localized in or around the brain, and for improved treatment of the tumors and neoplasia.

TECHNOLOGY FOCUS:

BIOTECHNOLOGY - Preferred Compound: In (I), the agent is chosen from therapeutic agent, diagnostic agent, marker of a disease of the CNS and a labeled monoclonal antibody which binds a marker of a CNS disorder. The therapeutic agent is chosen from protein, cytotoxic chemotherapeutic agent, protein nucleic acid, short interfering RNA (siRNA) molecule, antisense molecule and an expression construct comprising a nucleic acid that encodes a therapeutic protein of interest. The megalin-binding moiety and the agent of interest are directly linked to each other, or linked through a linker, where the linker is a peptide linker. The megalin-binding moiety is a moiety that is transcytosed in vivo, and is chosen from RAP, thyroglobulin, lipoprotein lipase, lactoferrin, apolipoprotein J/clusterin, apolipoprotein B, apolipoprotein E, tissue type plasminogen activator, urokinase plasminogen activator (uPA), plasminogen activator inhibitor-1 (PAI-1), vitamin D-binding protein, vitamin A/retinol-binding protein, beta2-microglobin, alpha1-microglobulin, vitamin B12/cobalamin plasma carrier protein, transcobalamin (TC)-B12, parathyroid hormone (PTH), insulin, epidermal growth factor (EGF), prolactin, albumin, apo H, transthyretin, lysozyme, cytochrome-c, alpha-amylase, Ca2+ and aprotinin, preferably RAP. In (I) or (II), the agent of interest is bound to the C-terminus of the megalin-binding moiety. The megalin-binding moiety and the agent of interest are each a protein and megalin-binding moiety is bound to the N-terminus of the agent of interest. When treating lysosomal storage disease, the agent is an enzyme deficient in the disease, e.g. aspartylglucosaminidase, acid lipase, cysteine transporter, Lamp-2, alpha-galactosidase A, acid ceramidase, alpha-L-fucosidase, beta-hexosaminidase A, GM2-activator deficiency, alpha-D-mannosidase, beta-D-mannosidase, arylsulfatase A, saposin B, neuraminidase, alpha-N-acetylglucosaminidase phosphotransferase, phosphotransferase gamma-subunit, L-iduronidase, iduronate-2-sulfatase, heparan-N-sulfatase, alpha-N-acetylglucosaminidase, acetylCoA:N-acetyltransferase, N-acetylglucosamine 6-sulfatase, galactose 6-sulfatase, beta-galactosidase, N-acetylgalactosamine 4-sulfatase, hyaluronoglucosaminidase, multiple sulfatases, palmitoyl protein thioesterase, tripeptidyl peptidase I, acid sphingomyelinase, cholesterol trafficking, cathepsin K, alpha-galactosidase B and sialic acid transporter.

Preferred Process: PC1 is administered to decrease amount of

storage granules present in the brain tissue or the meningeal tissue of the mammal, where the mammal is human. The symptoms are monitored through routine assessment of history, physical examination, echocardiography, electrocardiography, magnetic resonance imaging, polysomnography, skeletal survey, range of motion measurements, corneal photographs and skin biopsy. The mammal with the lysosomal storage disease (LSD) demonstrates 50% or less of a normal alpha-L-iduronidase activity. The administration of a megalin-binding moiety conjugated to a therapeutic agent results in normalization of developmental delay and regression, reduction in high pressure hydrocephalus, reduction in spinal cord compression, and reduction in number and/or size of perivascular cysts around the brain vessels. The method further involves inducing antigen specific tolerance prior to the enzyme replacement therapy. The antigen specific tolerance includes administration of an immunosuppressive agent such as cyclosporin A. The antigen specific tolerance further includes administration of an antiproliferative agent, which is chosen from nucleotide analog or an anti-metabolite. The antiproliferative agent is azathioprine. PC1 is useful for promoting the breakdown of glycosaminoglycan (GAG) in a brain cell of a subject having LSD, which involves administering to the subject PC1 comprising an enzyme deficient in LSD conjugated to a megalin-binding moiety to reduce the amount of GAG present in the brain cell as compared to the amount of GAG present in the cell prior to the administration. The brain cell is neuron, neuroglial cell or ependymal cell. The brain cell is a neuron, glial cell, microglial cell, astrocyte, oligodendroglial cell, perivascular cell, perithelial cell, meningeal cell, ependymal cell, arachnoid granulation cells arachnoid membrane, dura mater, pia mater and choroid plexus cell, preferably meningeal cell. The subject has high pressure hydrocephalus, and the administering reduces the amount of cerebrospinal fluid (CSF) in the meningeal tissue of the subject. The number of lysosomal storage granules in the cell are reduced as compared to the number of lysosomal storage granules present in a similar cell in the absence of administration of the conjugate. The number of lysosomal storage granules in the cell is reduced as compared to the number of lysosomal storage granules present in a similar cell treated with enzyme alone without conjugation to the megalin-binding moiety.

EXTENSION ABSTRACT:

ADMINISTRATION - PC1 is administered by intrathecal route into the CNS of the mammal, at a weekly dosage of 0.001-0.5 mg/kg body weight of the human suffering from the deficiency. PC1 is administered at a weekly dose of 0.01-5.0 mg/15 cc of CSF of the mammal suffering from a deficiency. PC1 is administered into cerebral ventricle, lumbar area or the cisterna magna. The intrathecal administration is achieved by use of an infusion pump. The intrathecal administration is continued over a period of at least several days (claimed). EXAMPLE - Preparation of receptor associated protein (RAP) fusions was carried out as follows. Expression construct for RAP-alpha-glucosidase (GAA) was introduced into an Lrp-deficient Chinese hamster ovarian (CHO) cell line (CHO13-5-1). The cells were cultivated in culture medium JRH 302 supplemented with L-glutamine (2 mM), gentamycin, amphotericin, G418 (800 microg/ml) and fetal calf serum (FCS) (2.5%). Recombinant clones were grown in T225 flasks prior to seeding into 1 liter Corning spinner flasks. Subsequently, harvests were collected every two days and medium was exchanged. RAP-GAA harvested in the medium from the spinner flasks was applied to a Blue-Sepharose column in low-salt buffer at neutral pH. Fusion was eluted with a linear salt gradient, and fractions containing fusion were loaded to a Heparin-Sepharose column and again eluted with a linear salt gradient. Eluted fractions containing activity were pooled and applied to a Phenyl-Sepharose column. RAP-GAA was eluted from the Phenyl-Sepharose column with a decreasing salt step gradient. Eluted fractions were run on sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) gel and stained to determine

relative percent purity. Based on gel analysis, peak activity fractions were 70% pure. Fractions were pooled, concentrated using a membrane and exchanged into phosphate buffered saline (PBS) at neutral pH.

FILE SEGMENT: CPI

MANUAL CODE: CPI: B04-C01C; B04-E06; B04-E07C; B04-E08; B04-E10; B04-G21; B04-H06A; B04-H15; B04-J03A; B04-J04; B04-J05; B04-L04; B04-L05; B04-N02; B04-N03A; B04-N04; B04-N05; B04-N06; B05-A01B; B06-D09; B12-K04A; B14-F01; B14-F02; B14-F06; B14-G02; B14-H01; B14-J01; B14-N10; B14-N16; B14-S01; B14-S13; D05-H12D2; D05-H12D8; D05-H12E

TEXT SEARCH PART 1

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=> fil agricola pascal caba biotechno wpix biosis dissabs esbio embase scisearch
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FILE 'PASCAL' ENTERED AT 11:04:29 ON 18 JUN 2010
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=> d que l130; d que l132; d que l135

L93        13980 SEA GALACTOSIDASE(A) A
L94          181 SEA RHGAA OR RH GAA
L96      1588404 SEA RECOMB?
L97        10410 SEA LYSOSOM? STORAGE DISEASE#
L98        41383 SEA POMPE OR POMPES
L99         2204 SEA GLYCOGEN STORAGE DISEASE TYPE(W)(2 OR II)
L104      933367 SEA PHOSPHORYLAT?
L105          33 SEA (GLUCOSE OXIDASE)(A) A
L106         646 SEA ASPARTYLGLUCOSAMINURIA
L107         479 SEA CHOLESTEROL ESTER STORAGE
L108        3878 SEA CYSTINOSIS
L109         187 SEA MANNOSIDASE DEFICIENCY
L110       12563 SEA MUCOPOLYSACCHARIDOS!S
L111        1301 SEA WOLMAN#
L112        1185 SEA FUCOSIDOS!S
L113        3225 SEA MUCOLIPIDOS!S
L114        1508 SEA SPHINGOLIPIDOS!S
L115       30549 SEA FABRY#
L116          52 SEA FARBER LIPOGRANULOMATOS!S
L117       17226 SEA GAUCHER?
L118        9810 SEA NIEMANN PICK#
L119        2325 SEA (GLOBOID CELL#)(2A) LEUKODYSTROP?
L120          60 SEA SULFATIDOS!S
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L121       6095 SEA GANGLIOSIDOS!S
L122       6139 SEA TAY SACHS
L123       2420 SEA SANDHOFF#
L124        682 SEA MULTIPLE SULFATASE DEFICIENC?
L125       4600 SEA METACHROMATIC(A) LEUKODYSTROPH?
L130          7 SEA ((L93(5A) L96) OR L94 OR L105) AND (L97 OR L98 OR L99 OR
                L106 OR L107 OR L108 OR L109 OR L110 OR L111 OR L112 OR L113
                OR L114 OR L115 OR L116 OR L117 OR L118 OR L119 OR L120 OR
                L121 OR L122 OR L123 OR L124 OR L125) AND L104
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L93       13980 SEA GALACTOSIDASE(A) A
L94         181 SEA RHGAA OR RH GAA
L96     1588404 SEA RECOMB?
L97       10410 SEA LYSOSOM? STORAGE DISEASE#
L98       41383 SEA POMPE OR POMPES
L99        2204 SEA GLYCOGEN STORAGE DISEASE TYPE(W)(2 OR II)
L100       7817 SEA RECEPTOR#(2A)(MANNOSE 6 PHOSPHATE OR (INSULIN LIKE GROWTH
                FACTOR OR IGF)(A)(TYPE(W)(2 OR II)))
L102      41248 SEA (ACETYL(W) GLUCOSAMINE OR ACETYLGLUCOSAMINE)/BI
L103     132565 SEA GALACTOSE
L105         33 SEA (GLUCOSE OXIDASE)(A) A
L106        646 SEA ASPARTYLGLUCOSAMINURIA
L107        479 SEA CHOLESTEROL ESTER STORAGE
L108       3878 SEA CYSTINOSIS
L109        187 SEA MANNOSIDASE DEFICIENCY
L110      12563 SEA MUCOPOLYSACCHARIDOS!S
L111       1301 SEA WOLMAN#
L112       1185 SEA FUCOSIDOS!S
L113       3225 SEA MUCOLIPIDOS!S
L114       1508 SEA SPHINGOLIPIDOS!S
L115      30549 SEA FABRY#
L116         52 SEA FARBER LIPOGRANULOMATOS!S
L117      17226 SEA GAUCHER?
L118       9810 SEA NIEMANN PICK#
L119       2325 SEA (GLOBOID CELL#)(2A) LEUKODYSTROP?
L120         60 SEA SULFATIDOS!S
L121       6095 SEA GANGLIOSIDOS!S
L122       6139 SEA TAY SACHS
L123       2420 SEA SANDHOFF#
L124        682 SEA MULTIPLE SULFATASE DEFICIENC?
L125       4600 SEA METACHROMATIC(A) LEUKODYSTROPH?
L131       8850 SEA (L100 AND (L102 OR L103)) OR (L102 AND L103)
L132          7 SEA ((L93(5A) L96) OR L94 OR L105) AND (L97 OR L98 OR L99 OR
                L106 OR L107 OR L108 OR L109 OR L110 OR L111 OR L112 OR L113
                OR L114 OR L115 OR L116 OR L117 OR L118 OR L119 OR L120 OR
                L121 OR L122 OR L123 OR L124 OR L125) AND L131
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L93       13980 SEA GALACTOSIDASE(A) A
L96     1588404 SEA RECOMB?
L98       41383 SEA POMPE OR POMPES
L99        2204 SEA GLYCOGEN STORAGE DISEASE TYPE(W)(2 OR II)
L134        202 SEA HUMAN(3A) L96(3A) L93
L135          1 SEA L134 AND (L98 OR L99)
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=> s l148 not l126

L149         12 L148 NOT L126        L126=INVENTOR SEARCH

=> fil hcapl; e lysosomal storage diseases+all/ct;d que l23; d que l33

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FILE COVERS 1907 - 18 Jun 2010  VOL 152 ISS 26
FILE LAST UPDATED: 17 Jun 2010  (20100617/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Apr 2010
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Apr 2010

HCAplus now includes complete International Patent Classification (IPC)
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E1           0   -->  Lysosomal storage diseases/CT
E2        1028     USE  Lysosomal storage disease/CT
********** END **********


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L9         4266 SEA FILE=HCAPLUS SPE=ON  ABB=ON  L7
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L33          20 SEA FILE=HCAPLUS SPE=ON  ABB=ON  (L17 OR L18 OR L11 OR L12 OR
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=> s l23,l33 not l29

L150        19 (L23 OR L33) NOT L29       L29=INVENTOR SEARCH


=> fil medl; d que l70; d que l74

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 FILE LAST UPDATED: 17 Jun 2010 (20100617/UP).  FILE COVERS 1947 TO DATE.

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 http://www.nlm.nih.gov/pubs/techbull/nd09/nd09_medline_data_changes_2010.html.

 The Medline file has been reloaded effective January 24, 2010.  See HELP
 RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

 See HELP RANGE before carrying out any RANGE search.


L59        3349 SEA FILE=MEDLINE SPE=ON  ABB=ON  ALPHA-GLUCOSIDASES/CT
L62       17870 SEA FILE=MEDLINE SPE=ON  ABB=ON  LYSOSOMAL STORAGE DISEASES+NT/
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L67        9132 SEA FILE=MEDLINE SPE=ON  ABB=ON  PROTEIN ENGINEERING/CT
L68      141392 SEA FILE=MEDLINE SPE=ON  ABB=ON  RECOMBINANT PROTEINS/CT
L69         438 SEA FILE=MEDLINE SPE=ON  ABB=ON  L59(L)GE/CT
L70          10 SEA FILE=MEDLINE SPE=ON  ABB=ON  L69 AND (L67 OR L68) AND L62
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L62       17870 SEA FILE=MEDLINE SPE=ON  ABB=ON  LYSOSOMAL STORAGE DISEASES+NT/
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L151         12 (L70 OR L74) NOT L64       L64=INVENTOR SEARCH


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PROCESSING COMPLETED FOR L151
PROCESSING COMPLETED FOR L150
PROCESSING COMPLETED FOR L149
L152         37 DUP REM L151 L150 L149 (6 DUPLICATES REMOVED)
                ANSWERS '1-12' FROM FILE MEDLINE
                ANSWERS '13-31' FROM FILE HCAPLUS
                ANSWERS '32-33' FROM FILE BIOTECHNO
                ANSWERS '34-36' FROM FILE WPIX
                ANSWER '37' FROM FILE DISSABS

=> d iall 1-12; d ibib ab hitind 13-31; d iall 32-33; d ifull 34-36; d iall 37

L152 ANSWER 1 OF 37     MEDLINE on STN
ACCESSION NUMBER:    2010073105     MEDLINE  Full-text
DOCUMENT NUMBER:     PubMed ID: 19690517
TITLE:               Immunomodulatory gene therapy prevents antibody formation
                     and lethal hypersensitivity reactions in murine pompe
                     disease.
AUTHOR:              Sun Baodong; Kulis Michael D; Young Sarah P; Hobeika Amy C;
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Li Songtao; Bird Andrew; Zhang Haoyue; Li Yifan; Clay Timothy M; Burks Wesley; Kishnani Priya S; Koeberl Dwight D
CORPORATE SOURCE: Department of Pediatrics, Division of Medical Genetics, Duke University Medical Center, Durham, North Carolina, USA.
CONTRACT NUMBER: R01 HL081122-01A1 (United States NHLBI NIH HHS)
R01 HL081122-01A1 (United States NHLBI NIH HHS)
SOURCE: Molecular therapy : the journal of the American Society of Gene Therapy, (2010 Feb) Vol. 18, No. 2, pp. 353-60.
Electronic Publication: 2009-08-18.
Journal code: 100890581. E-ISSN: 1525-0024. L-ISSN: 1525-0016.
Report No.: NLM-NIHMS153579 [Available on 02/01/11]; NLM-PMC2818301 [Available on 02/01/11].
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 201004
ENTRY DATE: Entered STN: 4 Feb 2010
Last Updated on STN: 23 Apr 2010
Entered Medline: 22 Apr 2010

ABSTRACT:
Infantile Pompe disease progresses to a lethal cardiomyopathy in absence of effective treatment. Enzyme-replacement therapy (ERT) with recombinant human acid alpha-glucosidase (rhGAA) has been effective in most patients with Pompe disease, but efficacy was reduced by high-titer antibody responses. Immunomodulatory gene therapy with a low dose adeno-associated virus (AAV) vector (2 x 10(10) particles) containing a liver-specific regulatory cassette significantly lowered immunoglobin G (IgG), IgG1, and IgE antibodies to GAA in Pompe disease mice, when compared with mock-treated mice (P < 0.05). AAV-LSPhGAApA had the same effect on GAA-antibody production whether it was given prior to, following, or simultaneously with the initial GAA injection. Mice given AAV-LSPhGAApA had significantly less decrease in body temperature (P < 0.001) and lower anaphylactic scores (P < 0.01) following the GAA challenge. Mouse mast cell protease-1 (MMCP-1) followed the pattern associated with hypersensitivity reactions (P < 0.05). Regulatory T cells (Treg) were demonstrated to play a role in the tolerance induced by gene therapy as depletion of Treg led to an increase in GAA-specific IgG (P < 0.001). Treg depleted mice were challenged with GAA and had significantly stronger allergic reactions than mice given gene therapy without subsequent Treg depletion (temperature: P < 0.01; symptoms: P < 0.05). Ubiquitous GAA expression failed to prevent antibody formation. Thus, immunomodulatory gene therapy could provide adjunctive therapy in lysosomal storage disorders treated by enzyme replacement.

CONTROLLED TERM: Animals
Antibody Formation: GE, genetics
*Antibody Formation: IM, immunology
Cell Line
Dependovirus: GE, genetics
*Dependovirus: PH, physiology
Enzyme Replacement Therapy: MT, methods
Enzyme-Linked Immunosorbent Assay
*Gene Therapy: MT, methods
*Glycogen Storage Disease Type II: IM, immunology
*Glycogen Storage Disease Type II: TH, therapy
Humans
Mice

Mice, Inbred C57BL
alpha-Glucosidases: GE, genetics
alpha-Glucosidases: PH, physiology
CHEMICAL NAME: EC 3.2.1.20 (GAA protein, human); EC 3.2.1.20 (alpha-Glucosidases)

L152 ANSWER 2 OF 37 MEDLINE on STN
ACCESSION NUMBER: 2009384502 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 19277015
TITLE: Glycoengineered acid alpha-glucosidase with improved efficacy at correcting the metabolic aberrations and motor function deficits in a mouse model of Pompe disease.
AUTHOR: Zhu Yunxiang; Jiang Ji-Lei; Gumlaw Nathan K; Zhang Jinhua; Bercury Scott D; Ziegler Robin J; Lee Karen; Kudo Mariko; Canfield William M; Edmunds Timothy; Jiang Canwen; Mattaliano Robert J; Cheng Seng H
CORPORATE SOURCE: Genzyme Corporation, Framingham, Massachusetts 01701-9322, USA.. yunxiang.zhu@genzyme.com
SOURCE: Molecular therapy : the journal of the American Society of Gene Therapy, (2009 Jun) Vol. 17, No. 6, pp. 954-63.
Electronic Publication: 2009-03-10.
Journal code: 100890581. E-ISSN: 1525-0024. L-ISSN: 1525-0016.
Report No.: NLM-PMC2835178.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200908
ENTRY DATE: Entered STN: 4 Jun 2009
Last Updated on STN: 8 Aug 2009
Entered Medline: 7 Aug 2009
ABSTRACT:
Improving the delivery of therapeutics to disease-affected tissues can increase their efficacy and safety. Here, we show that chemical conjugation of a synthetic oligosaccharide harboring mannose 6-phosphate (M6P) residues onto recombinant human acid alpha-glucosidase (rhGAA) via oxime chemistry significantly improved its affinity for the cation-independent mannose 6-phosphate receptor (CI-MPR) and subsequent uptake by muscle cells. Administration of the carbohydrate-remodeled enzyme (oxime-neo-rhGAA) into Pompe mice resulted in an approximately fivefold higher clearance of lysosomal glycogen in muscles when compared to the unmodified counterpart. Importantly, treatment of immunotolerized Pompe mice with oxime-neo-***rhGAA*** translated to greater improvements in muscle function and strength. Treating older, symptomatic Pompe mice also reduced tissue glycogen levels but provided only modest improvements in motor function. Examination of the muscle pathology suggested that the poor response in the older animals might have been due to a reduced regenerative capacity of the skeletal muscles. These findings lend support to early therapeutic intervention with a targeted enzyme as important considerations in the management of Pompe disease.
CONTROLLED TERM: Animals
Disease Models, Animal
Glycogen: ME, metabolism
*Glycogen Storage Disease Type II: DT, drug therapy
Glycogen Storage Disease Type II: ME, metabolism
Humans
*Mannosephosphates: CH, chemistry
Mice
Mice, Inbred C57BL
Muscle, Skeletal: DE, drug effects

Muscle, Skeletal: ME, metabolism
Muscle, Skeletal: PA, pathology
*Oligosaccharides: CH, chemistry
Protein Binding
*Protein Engineering: MT, methods
Receptor, IGF Type 2: ME, metabolism
alpha-Glucosidases: CH, chemistry
alpha-Glucosidases: GE, genetics
*alpha-Glucosidases: ME, metabolism
alpha-Glucosidases: PD, pharmacology
*alpha-Glucosidases: TU, therapeutic use

CAS REGISTRY NO.: 9005-79-2 (Glycogen)
CHEMICAL NAME: 0 (Mannosephosphates); 0 (Oligosaccharides); 0 (Receptor, IGF Type 2); EC 3.2.1.20 (GAA protein, human); EC 3.2.1.20 (alpha-Glucosidases)

L152 ANSWER 3 OF 37 MEDLINE on STN
ACCESSION NUMBER: 2009431009 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 19472353
TITLE: A novel mutation of the GAA gene in a Finnish late-onset Pompe disease patient: clinical phenotype and follow-up with enzyme replacement therapy.
AUTHOR: Korpela Mari P; Paetau Anders; Lofberg Mervi I; Timonen Marjut H; Lamminen Antti E; Kiuru-Enari Sari M K
CORPORATE SOURCE: Department of Neurology, Helsinki University Central Hospital, P.O. Box 340, Helsinki 00029, Finland.. marinposti@hotmial.com
SOURCE: Muscle & nerve, (2009 Jul) Vol. 40, No. 1, pp. 143-8. Journal code: 7803146. ISSN: 0148-639X. L-ISSN: 0148-639X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200908
ENTRY DATE: Entered STN: 23 Jun 2009
Last Updated on STN: 26 Aug 2009
Entered Medline: 25 Aug 2009

ABSTRACT:
Pompe disease is a rare, progressive disease leading to skeletal muscle weakness due to deficiency of the acid alpha-glucosidase (GAA) enzyme. Herein we report the first diagnosed Finnish patient with a phenotype compatible with the late-onset form of Pompe disease. Molecular genetic analysis of the GAA gene revealed a novel missense mutation, 1725C>A (Y575X), combined with a previously reported mutation, 1634C>T (P545L). Human recombinant alpha-glucosidase enzyme (alglucosidase-alpha) treatment was initiated for this patient at age 20 years. After 12 months she was no longer fully wheelchair-bound, and muscle strength had improved. No disease progression was visible on muscle magnetic resonance imaging of the lower limbs, and the energy state of the muscle cells increased by 46% on phosphorus magnetic resonance spectroscopy. Overall, our findings suggest that enzyme replacement therapy is indicated, even in patients with late-onset Pompe disease, to halt disease progression and improve the quality of daily life.

CONTROLLED TERM: Check Tags: Female
DNA Mutational Analysis
Electrocardiography
Electromyography: MT, methods
Electrons: DU, diagnostic use
Finland: EH, ethnology
Follow-Up Studies

Glycogen Storage Disease Type II: DI, diagnosis
*Glycogen Storage Disease Type II: DT, drug therapy
*Glycogen Storage Disease Type II: GE, genetics
Glycogen Storage Disease Type II: PP, physiopathology
Humans
Magnetic Resonance Imaging: MT, methods
Magnetic Resonance Spectroscopy: MT, methods
Muscle, Skeletal: PA, pathology
Muscle, Skeletal: PP, physiopathology
Muscle, Skeletal: RI, radionuclide imaging
Mutation: GE, genetics
Recombinant Proteins: TU, therapeutic use
Tyrosine: GE, genetics
Young Adult
*alpha-Glucosidases: GE, genetics
*alpha-Glucosidases: TU, therapeutic use

CAS REGISTRY NO.: 55520-40-6 (Tyrosine)
CHEMICAL NAME: 0 (Recombinant Proteins); EC 3.2.1.20 (alpha-Glucosidases)

L152 ANSWER 4 OF 37 MEDLINE on STN
ACCESSION NUMBER: 2008444480 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 18538603
TITLE: Biochemical and pharmacological characterization of different recombinant acid alpha-glucosidase preparations evaluated for the treatment of Pompe disease.
AUTHOR: McVie-Wylie A J; Lee K L; Qiu H; Jin X; Do H; Gotschall R; Thurberg B L; Rogers C; Raben N; O'Callaghan M; Canfield W; Andrews L; McPherson J M; Mattaliano R J
CORPORATE SOURCE: Biologics Research and Development, Genzyme Corporation, One Mountain Road, Framingham, MA 01701, USA.. alison.mcviewylie@genzyme.com
CONTRACT NUMBER: Z01 AR041099-17 (United States NIAMS NIH HHS)
SOURCE: Molecular genetics and metabolism, (2008 Aug) Vol. 94, No. 4, pp. 448-55. Electronic Publication: 2008-06-05. Journal code: 9805456. E-ISSN: 1096-7206. L-ISSN: 1096-7192.
Report No.: NLM-NIHMS151010; NLM-PMC2774491.
PUB. COUNTRY: United States
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200808
ENTRY DATE: Entered STN: 15 Jul 2008
Last Updated on STN: 15 Aug 2008
Entered Medline: 14 Aug 2008

ABSTRACT:
Pompe disease results in the accumulation of lysosomal glycogen in multiple tissues due to a deficiency of acid alpha-glucosidase (GAA). Enzyme replacement therapy for Pompe disease was recently approved in Europe, the U.S., Canada, and Japan using a recombinant human GAA (Myozyme, alglucosidase alfa) produced in CHO cells (CHO-GAA). During the development of alglucosidase alfa, we examined the in vitro and in vivo properties of CHO cell-derived ***rhGAA*** , an rhGAA purified from the milk of transgenic rabbits, as well as an experimental version of rhGAA containing additional mannose-6-phosphate intended to facilitate muscle targeting. Biochemical analyses identified differences in rhGAA N-termini, glycosylation types and binding properties to several carbohydrate receptors. In a mouse

model of Pompe disease, glycogen was more efficiently removed from the heart than from skeletal muscle for all enzymes, and overall, the CHO cell-derived ***rhGAA*** reduced glycogen to a greater extent than that observed with the other enzymes. The results of these preclinical studies, combined with biochemical characterization data for the three molecules described within, led to the selection of the CHO-GAA for clinical development and registration as the first approved therapy for Pompe disease.

CONTROLLED TERM: Animals
Antibodies: BL, blood
CHO Cells
Cells, Cultured
Cricetinae
Cricetulus
Drug Evaluation, Preclinical
Fibroblasts: ME, metabolism
Glycogen: ME, metabolism
Glycogen Storage Disease Type II: IM, immunology
Glycogen Storage Disease Type II: ME, metabolism
*Glycogen Storage Disease Type II: TH, therapy
Humans
Lectins, C-Type: ME, metabolism
Mannose-Binding Lectins: ME, metabolism
Mice
Oligosaccharides: CH, chemistry
Oligosaccharides: ME, metabolism
Protein Binding
Rabbits
Receptor, IGF Type 2: ME, metabolism
Receptors, Cell Surface: ME, metabolism
Recombinant Proteins: CH, chemistry
Recombinant Proteins: GE, genetics
Recombinant Proteins: IP, isolation & purification
Recombinant Proteins: ME, metabolism
Recombinant Proteins: PD, pharmacology
*alpha-Glucosidases: CH, chemistry
alpha-Glucosidases: GE, genetics
alpha-Glucosidases: ME, metabolism
*alpha-Glucosidases: PD, pharmacology

CAS REGISTRY NO.: 9005-79-2 (Glycogen)

CHEMICAL NAME: 0 (Antibodies); 0 (Lectins, C-Type); 0 (Mannose-Binding Lectins); 0 (Oligosaccharides); 0 (Receptor, IGF Type 2); 0 (Receptors, Cell Surface); 0 (Recombinant Proteins); 0 (mannose receptor); EC 3.2.1.20 (GAA protein, human); EC 3.2.1.20 (alpha-Glucosidases)

L152 ANSWER 5 OF 37 MEDLINE on STN

ACCESSION NUMBER: 2008361532 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 18525427

TITLE: Pompe disease: a review of the current diagnosis and treatment recommendations in the era of enzyme replacement therapy.

AUTHOR: Katzin Lara W; Amato Anthony A

CORPORATE SOURCE: Department of Neurology, University of South Florida, Tampa, FL 33606, USA.. lkatzin@hsc.usf.edu

SOURCE: Journal of clinical neuromuscular disease, (2008 Jun) Vol. 9, No. 4, pp. 421-31. Ref: 53
Journal code: 100887391. E-ISSN: 1537-1611. L-ISSN: 1522-0443.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200808
ENTRY DATE: Entered STN: 6 Jun 2008
Last Updated on STN: 29 Aug 2008
Entered Medline: 28 Aug 2008

ABSTRACT:
Pompe disease, or glycogen storage disease type II, is a rare autosomal recessive disorder caused by mutations in the gene that encodes for alpha-glucosidase. Presentation in infancy is associated with respiratory failure, cardiomyopathy, and severe muscle weakness. Juvenile- or adult-onset cases typically present with proximal muscle weakness and are associated with respiratory insufficiency or exertional dyspnea. Treatment, until recently, was focused on supportive measures, and infants diagnosed with Pompe disease usually died within the first year of life. The recent development of recombinant alpha-glucosidase has dramatically improved the life expectancy and quality of life of infantile-onset disease with improvements in respiratory and motor function observed in juvenile- or adult-onset cases. This review focuses on the presentation, pathogenesis, diagnosis, and treatment recommendations for Pompe disease in this new era of enzyme replacement therapy.

CONTROLLED TERM: *Enzymes: TU, therapeutic use
*Glycogen Storage Disease Type II: DI, diagnosis
Glycogen Storage Disease Type II: EN, enzymology
Glycogen Storage Disease Type II: GE, genetics
*Glycogen Storage Disease Type II: TH, therapy
Humans
Recombinant Proteins: TU, therapeutic use
alpha-Glucosidases: DF, deficiency
alpha-Glucosidases: GE, genetics
*alpha-Glucosidases: TU, therapeutic use
CHEMICAL NAME: 0 (Enzymes); 0 (Recombinant Proteins); EC 3.2.1.20 (alpha-Glucosidases)

L152 ANSWER 6 OF 37 MEDLINE on STN
ACCESSION NUMBER: 2007411288 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 17572127
TITLE: Differential muscular glycogen clearance after enzyme replacement therapy in a mouse model of Pompe disease.
AUTHOR: Hawes Michael L; Kennedy William; O'Callaghan Michael W; Thurberg Beth L
CORPORATE SOURCE: Department of Pathology, Genzyme Corporation, 1 Mountain Rd., P.O. Box 9322, Framingham, MA 01701-9322, USA.
SOURCE: Molecular genetics and metabolism, (2007 Aug) Vol. 91, No. 4, pp. 343-51. Electronic Publication: 2007-06-14. Journal code: 9805456. ISSN: 1096-7192. L-ISSN: 1096-7192.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200710
ENTRY DATE: Entered STN: 17 Jul 2007
Last Updated on STN: 25 Oct 2007
Entered Medline: 24 Oct 2007

ABSTRACT:
Glycogen storage disease in the alpha-glucosidase knockout(6neo(-)/6neo(-)) (GAA KO) mouse, a model of Pompe disease, results in the pathologic accumulation of glycogen primarily within skeletal myocytes and cardiomyocytes. Intravenous administration of recombinant human alpha-glucosidase (***rhGAA*** , Myozyme, aglucosidase alfa) can result in significant glycogen

clearance from both cardiomyocytes and skeletal myocytes, however, the degree of clearance varies from one skeletal muscle type to another. We sought to determine what role muscle fiber type predominance played in this variability. To examine this question in the GAA KO mouse model we delivered intravenous doses of 100 mg/kg rhGAA on Day 1, and Day 14, and harvested a variety of fast and slow twitch muscles on Day 28. We measured glycogen clearance, muscle fiber type content and capillary density by light microscopy with computer morphometry. Recombinant human-GAA administration resulted in differential clearance of glycogen in the various muscles examined. Slow twitch-predominant muscles cleared glycogen significantly more efficiently than fast twitch-predominant muscles. There was a strong correlation between capillary density and glycogen clearance (r=0.55), suggesting that at the high doses used in this study the differential glycogen clearance observed between muscles is largely due to differential bioavailability of rhGAA regulated by blood flow.

CONTROLLED TERM: Animals
Capillaries: EN, enzymology
Capillaries: PP, physiopathology
Disease Models, Animal
Glycogen Storage Disease Type II: EN, enzymology
Glycogen Storage Disease Type II: PA, pathology
*Glycogen Storage Disease Type II: TH, therapy
Humans
Mice
Mice, Knockout
Muscle, Skeletal: BS, blood supply
Muscle, Skeletal: EN, enzymology
*Muscle, Skeletal: ME, metabolism
Muscle, Skeletal: PA, pathology
alpha-Glucosidases: DF, deficiency
*alpha-Glucosidases: GE, genetics
*alpha-Glucosidases: TU, therapeutic use

CHEMICAL NAME: EC 3.2.1.20 (alpha-Glucosidases)

L152 ANSWER 7 OF 37 MEDLINE on STN

ACCESSION NUMBER: 2006497090 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 16846599

TITLE: Stabilising normal and mis-sense variant alpha-glucosidase.

AUTHOR: Kakavanos Revecca; Hopwood John J; Lang Debbie; Meikle Peter J; Brooks Doug A

CORPORATE SOURCE: Department of Genetic Medicine, Lysosomal Diseases Research Unit, Children Youth and Women's Health Service, North Adelaide, SA 5006, Australia.

SOURCE: FEBS letters, (2006 Aug 7) Vol. 580, No. 18, pp. 4365-70.
Electronic Publication: 2006-07-10.
Journal code: 0155157. ISSN: 0014-5793. L-ISSN: 0014-5793.

PUB. COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200609

ENTRY DATE: Entered STN: 23 Aug 2006
Last Updated on STN: 20 Sep 2006
Entered Medline: 19 Sep 2006

ABSTRACT:

alpha-Glucosidase (EC 3.2.1.3) is a lysosomal enzyme that hydrolyses alpha-1,4- and alpha-1,6-linkages of glycogen to produce free glucose. A deficiency in alpha-glucosidase activity results in glycogen storage disorder type II (GSD II), also called Pompe disease. Here, d-glucose was shown to be a competitive

inhibitor of alpha-glucosidase and when added to culture medium at 6.0 g/L increased the production of this protein by CHO-K1 expression cells and stabilised the enzyme activity. D-Glucose also prevented alpha-glucosidase aggregation/precipitation and increased protein yield in a modified purification scheme. In fibroblast cells, from adult-onset GSD II patients, D-glucose increased the residual level of alpha-glucosidase activity, suggesting that a structural analogue of d-glucose may be used for enzyme enhancement therapy.

CONTROLLED TERM: Animals
Butyric Acid: PD, pharmacology
CHO Cells
Cricetinae
Cricetulus
Enzyme Stability
Fibroblasts: EN, enzymology
Glucose: PD, pharmacology
*Glycogen Storage Disease Type II: EN, enzymology
Glycogen Storage Disease Type II: GE, genetics
Iduronidase: ME, metabolism
Kinetics
Mutation, Missense
Recombinant Proteins: BI, biosynthesis
Recombinant Proteins: IP, isolation & purification
Sulfatases: ME, metabolism
*alpha-Glucosidases: BI, biosynthesis
*alpha-Glucosidases: GE, genetics
alpha-Glucosidases: ME, metabolism

CAS REGISTRY NO.: 107-92-6 (Butyric Acid); 50-99-7 (Glucose)

CHEMICAL NAME: 0 (Recombinant Proteins); EC 3.1.6.- (Sulfatases); EC 3.2.1.20 (alpha-Glucosidases); EC 3.2.1.76 (Iduronidase)

L152 ANSWER 8 OF 37 MEDLINE on STN

ACCESSION NUMBER: 2006661103 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 17096293

TITLE: American Chemical Society 232nd National Meeting. Cancer and other therapeutic areas. 10-14 September 2006, San Francisco, CA, USA.

AUTHOR: Perry Letitia; Balfe Andrew

CORPORATE SOURCE: Thomson Scientific, Middlesex House, 34-42 Cleveland Street, London, W1T 4JE, UK.. letitia.perry@thomson.com

SOURCE: IDrugs : the investigational drugs journal, (2006 Nov) Vol. 9, No. 11, pp. 759-60.
Journal code: 100883655. ISSN: 1369-7056. L-ISSN: 1369-7056.

PUB. COUNTRY: England: United Kingdom

DOCUMENT TYPE: Conference; Conference Article; (CONGRESSES)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200701

ENTRY DATE: Entered STN: 14 Nov 2006
Last Updated on STN: 6 Jan 2007
Entered Medline: 5 Jan 2007

CONTROLLED TERM: Angiotensin II Type 1 Receptor Blockers: PD, pharmacology
Animals
Anti-Asthmatic Agents: PD, pharmacology
*Antineoplastic Agents: PD, pharmacology
Antineoplastic Agents: TU, therapeutic use
Chemistry
*Drugs, Investigational: PD, pharmacology
Drugs, Investigational: TU, therapeutic use

Glycogen Storage Disease Type II: DT, drug therapy
Hormone Antagonists: PD, pharmacology
Hormone Antagonists: TU, therapeutic use
Humans
Oxytocin: AI, antagonists & inhibitors
Receptors, Endothelin: AI, antagonists & inhibitors
Recombinant Proteins: TU, therapeutic use
Societies, Scientific
United States
alpha-Glucosidases: GE, genetics
alpha-Glucosidases: TU, therapeutic use

CAS REGISTRY NO.: 50-56-6 (Oxytocin)

CHEMICAL NAME: 0 (Angiotensin II Type 1 Receptor Blockers); 0 (Anti-Asthmatic Agents); 0 (Antineoplastic Agents); 0 (Drugs, Investigational); 0 (Hormone Antagonists); 0 (Receptors, Endothelin); 0 (Recombinant Proteins); EC 3.2.1.20 (GAA protein, human); EC 3.2.1.20 (alpha-Glucosidases)

L152 ANSWER 9 OF 37 MEDLINE on STN

ACCESSION NUMBER: 2003218482 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 12739885

TITLE: Induction of tolerance to a recombinant human enzyme, acid alpha-glucosidase, in enzyme deficient knockout mice.

AUTHOR: Raben Nina; Nagaraju Kanneboyina; Lee Alicia; Lu Nina; Rivera Yesenia; Jatkar Tejas; Hopwood John J; Plotz Paul H

CORPORATE SOURCE: Arthritis and Rheumatism Branch, NIAMS, National Institutes of Health, 9000 Rockville Pike, Clinical Center Bld. 10/9N244, Bethesda, MD 20892, USA.. rabenn@arb.niams.nih.gov

SOURCE: Transgenic research, (2003 Apr) Vol. 12, No. 2, pp. 171-8. Journal code: 9209120. ISSN: 0962-8819. L-ISSN: 0962-8819.

PUB. COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200401

ENTRY DATE: Entered STN: 13 May 2003
Last Updated on STN: 17 Jan 2004
Entered Medline: 16 Jan 2004

ABSTRACT:
When knockout mice are used to test the efficacy of recombinant human proteins, the animals often develop antibodies to the enzyme, precluding long-term pre-clinical studies. This has been a problem with a number of models, for example, the evaluation of gene or enzyme replacement therapies in a knockout model of glycogen storage disease type II (GSDII; Pompe syndrome). In this disease, the lack of acid alpha-glucosidase (GAA) results in lysosomal accumulation of glycogen, particularly in skeletal and cardiac muscle. Here, we report that in a GAA-deficient mouse model of GSDII, low levels of transgene-encoded human GAA expressed in skeletal muscle or liver dramatically blunt or abolish the immune response to human recombinant protein. Of two low expression transgenic lines, only the liver-expressing line exhibited a profound GAA deficiency in skeletal muscle and heart indistinguishable from that in the original knockouts. The study suggests that the induction of tolerance in animal models of protein deficiencies could be achieved by restricting the expression of a gene of interest to a particular, carefully chosen tissue.

CONTROLLED TERM: Animals
Autoantibodies: BI, biosynthesis
CHO Cells

Cricetinae
Disease Models, Animal
Glycogen Storage Disease Type II: TH, therapy
Humans
Liver: EN, enzymology
Mice
Mice, Knockout
Mice, Transgenic
Phenotype
Recombinant Proteins: IM, immunology
alpha-Glucosidases: GE, genetics
*alpha-Glucosidases: IM, immunology

CHEMICAL NAME: 0 (Autoantibodies); 0 (Recombinant Proteins); EC 3.2.1.20 (alpha-Glucosidases)

L152 ANSWER 10 OF 37 MEDLINE on STN

ACCESSION NUMBER: 2001306662 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11268285
TITLE: Intercellular transfer of the virally derived precursor form of acid alpha-glucosidase corrects the enzyme deficiency in inherited cardioskeletal myopathy Pompe disease.
AUTHOR: Pauly D F; Fraites T J; Toma C; Bayes H S; Huie M L; Hirschhorn R; Plotz P H; Raben N; Kessler P D; Byrne B J
CORPORATE SOURCE: Peter Belfer Cardiac Laboratory, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA.
CONTRACT NUMBER: HL27867 (United States NHLBI NIH HHS)
HL7227 (United States NHLBI NIH HHS)
N01-HD-2-3144 (United States NICHD NIH HHS)
SOURCE: Human gene therapy, (2001 Mar 20) Vol. 12, No. 5, pp. 527-38.
Journal code: 9008950. ISSN: 1043-0342. L-ISSN: 1043-0342.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 4 Jun 2001
Last Updated on STN: 4 Jun 2001
Entered Medline: 31 May 2001

ABSTRACT:
Pompe disease is a lethal cardioskeletal myopathy in infants and results from genetic deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA). Genetic replacement of the cDNA for human GAA (hGAA) is one potential therapeutic approach. Three months after a single intramuscular injection of 10(8) plaque-forming units (PFU) of E1-deleted adenovirus encoding human GAA (Ad-hGAA), the activity in whole muscle lysates of immunodeficient mice is increased to 20 times the native level. Direct transduction of a target muscle, however, may not correct all deficient cells. Therefore, the amount of enzyme that can be transferred to deficient cells from virally transduced cells was studied. Fibroblasts from an affected patient were transduced with AdhGAA, washed, and plated on transwell culture dishes to serve as donors of recombinant enzyme. Deficient fibroblasts were plated as acceptor cells, and were separated from the donor monolayer by a 22-microm pore size filter. Enzymatic and Western analyses demonstrate secretion of the 110-kDa precursor form of hGAA from the donor cells into the culture medium. This recombinant, 110-kDa species reaches the acceptor cells, where it can be taken up by mannose 6-phosphate receptor-mediated endocytosis. It then trafficks to lysosomes,

where Western analysis shows proteolytic processing to the 76- and 70-kDa lysosomal forms of the enzyme. Patient fibroblasts receiving recombinant hGAA by this transfer mechanism reach levels of enzyme activity that are comparable to normal human fibroblasts. Skeletal muscle cell cultures from an affected patient were also transduced with Ad-hGAA. Recombinant hGAA is identified in a lysosomal location in these muscle cells by immunocytochemistry, and enzyme activity is transferred to deficient skeletal muscle cells grown in coculture. Transfer of the precursor protein between muscle cells again occurs via mannose 6-phosphate receptors, as evidenced by competitive inhibition with 5 mM mannose 6-phosphate. In vivo studies in GAA-knockout mice demonstrate that hepatic transduction with adenovirus encoding either murine or human GAA can provide a depot of recombinant enzyme that is available to heart and skeletal muscle through this mechanism. Taken together, these data show that the mannose 6-phosphate receptor pathway provides a useful strategy for cell-to-cell distribution of virally derived recombinant GAA.

CONTROLLED TERM: Adenoviridae: GE, genetics
Animals
Blotting, Western
Cells, Cultured
Coculture Techniques
DNA, Complementary: ME, metabolism
Fibroblasts: ME, metabolism
*Gene Therapy: MT, methods
*Gene Transfer Techniques
*Glycogen Storage Disease Type II: GE, genetics
*Glycogen Storage Disease Type II: TH, therapy
Humans
Immunohistochemistry
Lysosomes: ME, metabolism
Mannosephosphates: ME, metabolism
Mice
Mice, Knockout
Mice, Nude
Muscle, Skeletal: CY, cytology
Myocardium: ME, metabolism
Placenta: ME, metabolism
Receptor, IGF Type 2: ME, metabolism
Recombinant Proteins: ME, metabolism
Time Factors
Transduction, Genetic
*alpha-Glucosidases: GE, genetics

CAS REGISTRY NO.: 3672-15-9 (mannose-6-phosphate)

CHEMICAL NAME: 0 (DNA, Complementary); 0 (Mannosephosphates); 0 (Receptor, IGF Type 2); 0 (Recombinant Proteins); EC 3.2.1.20 (alpha-Glucosidases)

L152 ANSWER 11 OF 37 MEDLINE on STN

ACCESSION NUMBER: 1998409512 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 9736785

TITLE: Recombinant human acid alpha-glucosidase: high level production in mouse milk, biochemical characteristics, correction of enzyme deficiency in GSDII KO mice.

AUTHOR: Bijvoet A G; Kroos M A; Pieper F R; Van der Vliet M; De Boer H A; Van der Ploeg A T; Verbeet M P; Reuser A J

CORPORATE SOURCE: Department of Clinical Genetics, Erasmus University, PO Box 1738, 3000 DR Rotterdam, The Netherlands.

SOURCE: Human molecular genetics, (1998 Oct) Vol. 7, No. 11, pp. 1815-24.
Journal code: 9208958. ISSN: 0964-6906. L-ISSN: 0964-6906.

PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 15 Jan 1999
Last Updated on STN: 15 Jan 1999
Entered Medline: 1 Dec 1998

ABSTRACT:
Glycogen storage disease type II (GSDII) is caused by lysosomal acid alpha-glucosidase deficiency. Patients have a rapidly fatal or slowly progressive impairment of muscle function. Enzyme replacement therapy is under investigation. For large-scale, cost-effective production of recombinant human acid alpha-glucosidase in the milk of transgenic animals, we have fused the human acid alpha-glucosidase gene to 6.3 kb of the bovine alphaS1-casein gene promoter and have tested the performance of this transgene in mice. The highest production level reached was 2 mg/ml. The major fraction of the purified recombinant enzyme has a molecular mass of 110 kDa and resembles the natural acid alpha-glucosidase precursor from human urine and the recombinant precursor secreted by CHO cells, with respect to pH optimum, Km, Vmax, N-terminal amino acid sequence and glycosylation pattern. The therapeutic potential of the recombinant enzyme produced in milk is demonstrated in vitro and in vivo. The precursor is taken up in a mannose 6-phosphate receptor-dependent manner by cultured fibroblasts, is converted to mature enzyme of 76 kDa and depletes the glycogen deposit in fibroblasts of patients. When injected intravenously, the milk enzyme corrects the acid alpha-glucosidase deficiency in heart and skeletal muscle of GSDII knockout mice.

CONTROLLED TERM: Check Tags: Female
Animals
CHO Cells
Cattle
Cricetinae
Fibroblasts: DE, drug effects
*Glycogen Storage Disease Type II: DT, drug therapy
Humans
Mammary Glands, Animal: ME, metabolism
Mice
Mice, Knockout
Mice, Transgenic
*Milk: EN, enzymology
*Recombinant Proteins: GE, genetics
Recombinant Proteins: ME, metabolism
Recombinant Proteins: PD, pharmacology
Transgenes
alpha-Glucosidases: DF, deficiency
*alpha-Glucosidases: GE, genetics
*alpha-Glucosidases: ME, metabolism

CHEMICAL NAME: 0 (Recombinant Proteins); EC 3.2.1.20 (alpha-Glucosidases)

L152 ANSWER 12 OF 37 MEDLINE on STN
ACCESSION NUMBER: 1998409498 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9736771
TITLE: Adenovirus-mediated transfer of the acid alpha-glucosidase gene into fibroblasts, myoblasts and myotubes from patients with glycogen storage disease type II leads to high level expression of enzyme and corrects glycogen accumulation.
AUTHOR: Nicolino M P; Puech J P; Kremer E J; Reuser A J; Mbebi C; Verdiere-Sahuque M; Kahn A; Poenaru L
CORPORATE SOURCE: Laboratoire de Genetique, Universite Rene Descartes (Paris

V), CHU Cochin-Port Royal.

SOURCE: Human molecular genetics, (1998 Oct) Vol. 7, No. 11, pp. 1695-702.
Journal code: 9208958. ISSN: 0964-6906. L-ISSN: 0964-6906.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 15 Jan 1999
Last Updated on STN: 15 Jan 1999
Entered Medline: 1 Dec 1998

ABSTRACT:
Glycogen storage disease type II (GSD II) is an autosomal recessive disorder caused by defects in the lysosomal acid alpha-glucosidase (GAA) gene. We investigated the feasibility of using a recombinant adenovirus containing the human GAA gene under the control of the cytomegalovirus promoter (AdCMV-GAA) to correct the enzyme deficiency in different cultured cells from patients with the infantile form of GSD II. In GAA-deficient fibroblasts infected with AdCMV-GAA, transduction and transcription of the human transgene resulted in de novo synthesis of GAA protein. The GAA enzyme activity was corrected from the deficient level to 12 times the activity of normal cells. The transduced cells overexpressed the 110 kDa precursor form of GAA, which was secreted into the culture medium and was taken up by recipient cells. The recombinant GAA protein was correctly processed and was active on both an artificial substrate 4-methylumbelliferyl-alpha-D-glucopyranoside (4MUG) and glycogen. In GAA-deficient muscle cells, a significant increase in cellular enzyme level, approximately 20-fold higher than in normal cells, was also observed after viral treatment. The transduced muscle cells were also able to efficiently secrete the recombinant GAA. Moreover, transfer of the human transgene resulted in normalization of cellular glycogen content with clearance of glycogen from lysosomes, as assessed by electron microscopy, in differentiated myotubes. These results demonstrate phenotypic correction of cultured skeletal muscle from a patient with infantile-onset GSD II using a recombinant adenovirus. We conclude that adenovirus-mediated gene transfer might be a suitable model system for further in vivo studies on delivering GAA to GSD II muscle, not only by direct cell targeting but also by a combination of secretion and uptake mechanisms.

CONTROLLED TERM: *Adenoviridae: GE, genetics
Blotting, Western
Cells, Cultured
Fibroblasts: ME, metabolism
Gene Therapy: MT, methods
*Gene Transfer Techniques
Glycogen: ME, metabolism
Glycogen Storage Disease Type II: GE, genetics
*Glycogen Storage Disease Type II: TH, therapy
Humans
Muscle, Skeletal: CY, cytology
Muscle, Skeletal: ME, metabolism
Recombinant Proteins: GE, genetics
Recombinant Proteins: ME, metabolism
Recombinant Proteins: PK, pharmacokinetics
Transduction, Genetic
*alpha-Glucosidases: GE, genetics
*alpha-Glucosidases: ME, metabolism
alpha-Glucosidases: PK, pharmacokinetics
CAS REGISTRY NO.: 9005-79-2 (Glycogen)
CHEMICAL NAME: 0 (Recombinant Proteins); EC 3.2.1.20 (alpha-Glucosidases)

L152 ANSWER 13 OF 37 HCAPLUS COPYRIGHT 2010 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2004:796069 HCAPLUS Full-text
DOCUMENT NUMBER: 142:32657
TITLE: Methotrexate reduces antibody responses to recombinant human α-galactosidase A therapy in a mouse model of Fabry disease
AUTHOR(S): Garman, R. D.; Munroe, K.; Richards, S. M.
CORPORATE SOURCE: Immunology Laboratory, Cell and Protein Therapeutics R+D, Genzyme Corporation, Framingham, MA, USA
SOURCE: Clinical and Experimental Immunology (2004), 137(3), 496-502
CODEN: CEXIAL; ISSN: 0009-9104
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Therapeutic enzymes are often recognized as foreign by the immune system of patients undergoing enzyme replacement therapy. The antibodies that develop may alter pharmacokinetics and biodistribution of the therapeutic protein, may be able to neutralize the activity of the enzyme, or may cause immune reactions in certain patients. We have explored treatment regimens to reduce the antibody response to human α-galactosidase A (r-hαGAL) in Fabry (αGAL knock-out) and normal BALB/c mice. A wide variety of treatment modalities were tested, including high dose tolerance induction; increased frequency of therapeutic doses and immunosuppressive drugs in combination with administration of enzyme. The most substantial effects were observed in mice injected i.v. with r-hαGAL in combination with methotrexate (MTX), which significantly lowered r-hαGAL-specific serum antibody levels. A short course of treatment with MTX was able to reduce antibody and spleen cell proliferative responses to long-term r-hαGAL treatment. MTX was able to suppress the development of r-hαGAL-specific IgG in antigen-primed mice. However, MTX was not effective in dampening robust ongoing antibody responses. These expts. provide a framework for the design of clin. protocols to prevent the drug-specific antibody responses of patients undergoing enzyme replacement therapy.

CC 1-7 (Pharmacology)

IT Fabry disease
Human
Immunosuppressants
(methotrexate reduces antibody responses to r-hα-galactosidase A therapy in Fabry disease)

OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L152 ANSWER 14 OF 37 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2009:92375 HCAPLUS Full-text
DOCUMENT NUMBER: 151:139778
TITLE: Long-Term Effects of Enzyme Replacement Therapy on Fabry Cardiomyopathy
AUTHOR(S): Weidemann, Frank; Niemann, Markus; Breunig, Frank; Herrmann, Sebastian; Beer, Meinrad; Stoerk, Stefan; Voelker, Wolfram; Ertl, Georg; Wanner, Christoph; Strotmann, Joerg

CORPORATE SOURCE: Department of Medicine, Divisions of Cardiology and Nephrology, University Hospital, Wuerzburg, 97080, Germany
SOURCE: Circulation (2009), 119(4), 524-529
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background: Enzyme replacement therapy with recombinant α-galactosidase A reduces left ventricular hypertrophy and improves regional myocardial function in patients with Fabry disease during short-term treatment. Whether enzyme replacement therapy is effective in all stages of Fabry cardiomyopathy during long-term follow-up is unknown. Methods and Results: We studied 32 Fabry patients over a period of 3 years regarding disease progression and clin. outcome under enzyme replacement therapy. Regional myocardial fibrosis was assessed by magnetic resonance imaging late-enhancement technique. Echocardiog. myocardial mass was calculated with the Devereux formula, and myocardial function was quantified by ultrasonic strain-rate imaging. In addition, exercise capacity was measured by bicycle stress test. All measurements were repeated at yearly intervals. At baseline, 9 patients demonstrated at least 2 fibrotic left ventricular segments (severe myocardial fibrosis), 11 had 1 left ventricular segment affected (mild fibrosis), and 12 were without fibrosis. In patients without fibrosis, enzyme replacement therapy resulted in a significant reduction in left ventricular mass (238±42 g at baseline, 202±46 g at 3 years; P for trend <0.001), an improvement in myocardial function (systolic radial strain rate, 2.3±0.4 and 2.9±0.6 s-1, resp.; P for trend=0.045), and a higher exercise capacity obtained by bicycle stress exercise (106±14 and 122±26 W, resp.; P for trend=0.014). In contrast, patients with mild or severe fibrosis showed a minor reduction in left ventricular hypertrophy and no improvement in myocardial function or exercise capacity. Conclusions: These data suggest that treatment of Fabry cardiomyopathy with recombinant α-galactosidase A should best be started before myocardial fibrosis has developed to achieve long-term improvement in myocardial morphol. and function and exercise capacity.

CC 1-8 (Pharmacology)

ST enzyme replacement therapy recombinant alpha galactosidase A Fabry cardiomyopathy; cardioprotectant myocardial fibrosis exercise

IT Cardiovascular agents
Cytoprotective agents
(cardioprotective agents; early enzyme replacement therapy with recombinant α-galactosidase A showed long-term improvements in cardiac morphol., function and exercise capacity in patient with Fabry cardiomyopathy showing no or little myocardial fibrosis)

IT Exercise
(early enzyme replacement therapy with recombinant α-galactosidase A showed long-term improvement in exercise capacity in patient with Fabry cardiomyopathy showing no or little myocardial fibrosis)

IT Cardiomyopathy
Fabry disease
Human
(early enzyme replacement therapy with recombinant α-galactosidase A showed long-term improvements in cardiac morphol., function and exercise capacity in patient with Fabry cardiomyopathy showing no or little myocardial fibrosis)

IT Therapy
(enzyme therapy; early enzyme replacement therapy with

recombinant α-galactosidase A showed long-term improvements in cardiac morphol., function and exercise capacity in patient with Fabry cardiomyopathy showing no or little myocardial fibrosis)

IT Heart disease
(fibrosis; early enzyme replacement therapy with recombinant α-galactosidase A showed long-term improvements in cardiac morphol., function and exercise capacity in patient with Fabry cardiomyopathy showing no or little myocardial fibrosis)

IT Ventricular hypertrophy
(left; early ERT with recombinant α-galactosidase A reduced left ventricular hypertrophy but did not improve myocardial function or exercise capacity in patient with Fabry cardiomyopathy showing no or little myocardial fibrosis)

IT Cell wall
(septum; early enzyme replacement therapy with recombinant α-galactosidase A showed long-term improvements in cardiac morphol., function and exercise capacity in patient with Fabry cardiomyopathy showing no or little myocardial fibrosis)

IT 9025-35-8, α-Galactosidase A
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(early enzyme replacement therapy with recombinant α-galactosidase A showed long-term improvements in cardiac morphol., function and exercise capacity in patient with Fabry cardiomyopathy showing no or little myocardial fibrosis)

OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L152 ANSWER 15 OF 37 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2009:494892 HCAPLUS Full-text

DOCUMENT NUMBER: 151:373512

TITLE: Decline of plasma brain natriuretic peptide during enzyme replacement therapy in a female patient with heterozygous Fabry's disease

AUTHOR(S): Masugata, Hisashi; Senda, Shoichi; Goda, Fuminori; Yamagami, Ayumu; Okuyama, Hiroyuki; Kohno, Takeaki; Hosomi, Naohisa; Yukiiri, Kazushi; Noma, Takahisa; Murao, Koji; Kohno, Masakazu; Itoh, Susumu

CORPORATE SOURCE: Department of Integrated Medicine, Kagawa University, Kagawa, Japan

SOURCE: Tohoku Journal of Experimental Medicine (2009), 217(3), 169-174
CODEN: TJEMAO; ISSN: 0040-8727

PUBLISHER: Tohoku University Medical Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB There are no data regarding changes in plasma brain natriuretic peptide (BNP) levels in patients with Fabry's diseases during enzyme replacement therapy (ERT). We describe a patient with Fabry's disease who demonstrated the improvement in plasma brain BNP levels in response to ERT. Fabry's disease is an X-linked lysosomal storage disorder caused by a deficiency of the enzyme α-galactosidase A, which results in progressive intracellular accumulation of globotriaosylceramide (Gb3) in various organs including the heart. Cardiac involvement is frequent in Fabry's disease, resulting in cardiac dysfunction due to hypertrophic changes of the myocardium and thickening of the valves. Although ERT has been reported to improve cardiac function, no consensus has

been reached regarding the effectiveness of ERT in female patients with heterozygous Fabry's disease. We report a 44-yr-old woman having heterozygous Fabry's disease, who showed mitral valve thickening and regurgitation on echocardiogram. ERT was performed by i.v. infusion of recombinant α-galactosidase A every 2 wk. We assessed the influences of ERT on cardiac function by measuring echocardiograhic parameters and monitoring BNP levels, which show treatment-induced drop in patients with heart failure. Although her cardiac function and mitral regurgitation assessed by echocardiog. had not improved 18 mo after the beginning of ERT, the plasma BNP level, which was 91.5 pg/mL before ERT, fell to 18.9 pg/mL. In conclusion, plasma BNP levels may be useful for evaluating the effectiveness of ERT for heterozygous Fabry's disease, even in patients who demonstrate no improvement in echocardiog. parameters of cardiac structure and function.

CC 1-8 (Pharmacology)

IT Mitral valve insufficiency
(decline in plasma brain natriuretic peptide level but no improvement in mitral regurgitation was observed during enzyme replacement therapy with recombinant α-galactosidase A in female patient with heterozygous Fabry's disease)

IT Fabry disease
Human
Prognosis
(decline in plasma brain natriuretic peptide level during enzyme replacement therapy with recombinant α-galactosidase A suggested its use for evaluating effectiveness of treatment in female patient with heterozygous Fabry's disease)

IT Therapy
(enzyme therapy; decline in plasma brain natriuretic peptide level during enzyme replacement therapy with recombinant α-galactosidase A suggested its use for evaluating effectiveness of treatment in female patient with heterozygous Fabry's disease)

IT 114471-18-0, Brain natriuretic peptide
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(decline in plasma brain natriuretic peptide level during enzyme replacement therapy with recombinant α-galactosidase A suggested its use for evaluating effectiveness of treatment in female patient with heterozygous Fabry's disease)

IT 9025-35-8, α-Galactosidase A
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(decline in plasma brain natriuretic peptide level during enzyme replacement therapy with recombinant α-galactosidase A suggested its use for evaluating effectiveness of treatment in female patient with heterozygous Fabry's disease)

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L152 ANSWER 16 OF 37 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2008:1471726 HCAPLUS Full-text
DOCUMENT NUMBER: 150:71814
TITLE: Preparing additionally glycosylated recombinant human α-galactosidase and its use for treatment of Fabry's disease
INVENTOR(S): Oh, Du Byeong; Lee, Jeong Mi; Kim, Seung Ho; Son, Yeong Su; Park, Heung Rok
PATENT ASSIGNEE(S): Isu Abxis Co., Ltd., S. Korea
SOURCE: Repub. Korean Kongkae Taeho Kongbo, 19pp.

CODEN: KRXXA7
DOCUMENT TYPE: Patent
LANGUAGE: Korean
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
KR 2008105735	A	20081204	KR 2007-53712	20070601
PRIORITY APPLN. INFO.:			KR 2007-53712	20070601

AB This invention provides a method of preparing addnl. glycosylated recombinant human α-galactosidase. The α-galactosidase was prepared by coexpressing of human α-galactosidase, dihydrofolate reductase and methotrexate in CHO cells, isolating the α-galactosidase, treating the enzyme with α-2,3-sialyltransferase, β-1,4-galactosyltransferase, CMP-N-acetylneuramic acid and MnCl2. By the method, the saccharide chain structure of the recombinant alpha-galactosidase (used as the enzyme therapy agent for Fabry's disease) is changed, and sialic acid (N-acetylneuraminic acid) is added to the saccharide chain terminals. The addnl. glycosylated recombinant alpha-galactosidase has high in-vivo stability and high therapy efficiency.

CC 3-2 (Biochemical Genetics)
Section cross-reference(s): 7, 13

ST glycosylated recombinant human alpha galactosidase

IT Animal cell line
(CHO; preparing addnl. glycosylated recombinant human α-galactosidase and its use for treatment of Fabry disease)

IT Therapy
(enzyme therapy; preparing addnl. glycosylated recombinant human α-galactosidase and its use for treatment of Fabry disease)

IT Fabry disease
Genetic engineering
Glycosylation
Human
(preparing addnl. glycosylated recombinant human α-galactosidase and its use for treatment of Fabry disease)

IT Carbohydrates
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sugar chain; preparing addnl. glycosylated recombinant human α-galactosidase and its use for treatment of Fabry disease)

IT 9025-35-8P
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(glycosylated; preparing addnl. glycosylated recombinant human α-galactosidase and its use for treatment of Fabry disease)

IT 59-05-2P, Methotrexate 9002-03-3P, Dihydrofolate reductase
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparing addnl. glycosylated recombinant human α-galactosidase and its use for treatment of Fabry disease)

IT 3063-71-6, CMP-NeuAc 7773-01-5, Manganese chloride (MnCl2) 9054-94-8, β-1,4-Galactosyltransferase 77537-85-0, α

-2,3-Sialyltransferase
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparing addnl. glycosylated recombinant human α-galactosidase and its use for treatment of Fabry disease)

IT 1093696-80-0 1093696-81-1 1093696-82-2 1093696-83-3
RL: PRP (Properties)
(unclaimed sequence; preparing addnl. glycosylated recombinant human α-galactosidase and its use for treatment of Fabry disease)

L152 ANSWER 17 OF 37 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2009:388285 HCAPLUS Full-text
DOCUMENT NUMBER: 151:259401
TITLE: Safety and efficacy of enzyme replacement therapy in the nephropathy of Fabry disease
AUTHOR(S): Fervenza, Fernando C.; Torra, Roser; Warnock, David G.
CORPORATE SOURCE: Division of Nephrology and Hypertension, Mayo Clinic College of Medicine, Rochester, MN, USA
SOURCE: Biologics: Targets & Therapy (2008), 2(4), 823-843
CODEN: BTTICT; ISSN: 1177-5491
PUBLISHER: Dove Medical Press (NZ) Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Kidney involvement with progressive loss of kidney function (Fabry nephropathy) is an important complication of Fabry disease, an X-linked lysosomal storage disorder arising from deficiency of α-galactosidase activity. Clin. trials have shown that enzyme replacement therapy (ERT) with recombinant human α-galactosidase clears globotriaosylceramide from kidney cells, and can stabilize kidney function in patients with mild to moderate Fabry nephropathy. Recent trials show that patients with more advanced Fabry nephropathy and overt proteinuria do not respond as well to ERT alone, but can benefit from anti-proteinuric therapy given in conjunction with ERT. This review focuses on the use of enzyme replacement therapy with agalsidase-alfa and agalsidase-beta in adults with Fabry nephropathy. The current results are reviewed and evaluated. The issues of dosing of enzyme replacement therapy, the use of adjunctive agents to control urinary protein excretion, and the individual factors that affect disease severity are reviewed.

CC 1-0 (Pharmacology)

IT Fabry disease
Human
Kidney disease
(enzyme replacement therapy with agalsidase-α and -β may be safe and effective in adult patient with nephropathy of Fabry disease)

IT Cytoprotective agents
(renoprotective agents; enzyme replacement therapy using recombinant human α-galactosidase cleared globotriaosylceramide from kidney cell and improved renal function patient with mild to moderate Fabry nephropathy)

IT 71965-57-6, Globotriaosylceramide
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enzyme replacement therapy using recombinant human α-galactosidase cleared globotriaosylceramide from kidney cell and improved renal function patient with mild to moderate Fabry nephropathy)

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

REFERENCE COUNT: 94 THERE ARE 94 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L152 ANSWER 18 OF 37 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2007:1344990 HCAPLUS Full-text

DOCUMENT NUMBER: 148:509753

TITLE: Establishment of immortalized Schwann cells from Fabry mice and their low uptake of recombinant .alpha.-galactosidase

AUTHOR(S): Kawashima, Ikuo; Watabe, Kazuhiko; Tajima, Youichi; Fukushige, Tomoko; Kanzaki, Tamotsu; Kanekura, Takuro; Sugawara, Kanako; Ohyanagi, Naho; Suzuki, Toshihiro; Togawa, Tadayasu; Sakuraba, Hitoshi

CORPORATE SOURCE: Department of Clinical Genetics, The Tokyo Metropolitan Institute of Medical Science, Tokyo Metropolitan Organization for Medical Research, Tokyo, Japan

SOURCE: Journal of Human Genetics (2007), 52(12), 1018-1025 CODEN: JHGEFR; ISSN: 1434-5161

PUBLISHER: Springer Japan

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Peripheral neuropathy is one of the important manifestations of Fabry disease. Enzyme replacement therapy with presently available recombinant α-galactosidases does not always improve the Fabry neuropathy. But the reason has not been determined yet. We established a Schwann cell line from Fabry mice, characterized it, and then examined the uptake of α-galactosidase by cells and its effect on the degradation of accumulated substrate. The cells exhibited a distinct Schwann cell morphol. and biochem. phenotype (α-Galactosidase activity was deficient, and numerous cytoplasmic inclusion bodies were present in the cells). A recombinant α-galactosidase added to the culture medium was incorporated into the cultured Fabry Schwann cells dose dependently. But the increase in cell-associated enzyme activity was less than that in the cases of human and mouse Fabry fibroblasts. The administration of a high dose of the enzyme improved the pathol. changes in cells, although a low dose of it did not. Cellular uptake of the enzyme was strongly inhibited in the presence of mannose 6-phosphate. This suggests that the enzyme is incorporated via cation-independent mannose 6-phosphate receptors in Schwann cells. The low expression of cation-independent mannose 6-phosphate receptors in Schwann cells must be one of the reasons their uptake of the present enzymes was low. The administration of a high dose of the enzyme or the development of an enzyme containing many mannose 6-phosphate residues is required to improve Fabry neuropathy.

CC 1-11 (Pharmacology)
Section cross-reference(s): 13

IT Fibroblast
Human
(immortalized Schwann cells from Fabry mouse compared to human Fabry fibroblast showed low uptake of α-galactosidase, Replagal and Fabrazyme)

IT Cell immortalization
Cell morphology
Fabry disease
Schwann cell
(immortalized Schwann cells from Fabry mouse were characterized and exhibited low uptake of Replagal and Fabrazyme)

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L152 ANSWER 19 OF 37 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2006:297538 HCAPLUS Full-text
DOCUMENT NUMBER: 145:284971
TITLE: Clinical benefit of enzyme replacement therapy in Fabry disease
AUTHOR(S): Breunig, F.; Weidemann, F.; Strotmann, J.; Knoll, A.; Wanner, C.
CORPORATE SOURCE: Department of Medicine, Division of Nephrology, University Hospital Wuerzburg, Wuerzburg, 97080, Germany
SOURCE: Kidney International (2006), 69(7), 1216-1221
CODEN: KDYIA5; ISSN: 0085-2538
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Enzyme replacement therapy (ERT) with recombinant human α-galactosidase A (r-hαGalA) enhances microvascular globotriaosylceramide clearance and improves clin. symptoms in patients with Fabry disease. We evaluated whether these effects are translated into a long-term benefit of kidney and heart function. We did a single center, prospective, open label study in 26 patients with Fabry disease (one early death, follow-up in 25 patients). r-α-GalA was administered in a dosage of 1 mg/kg body weight every second week. The effect of therapy on clin. end points (death, cardiac and cerebrovascular event, renal failure), cardiac and renal function monitored by Doppler echocardiog., 99Tc-GFR, and proteinuria was investigated. After a mean treatment time of 23±8 mo, nine patients experienced 12 end points, including two deaths. All end points occurred in patients with impaired renal function (n=16; GFR 71±17 mL/min/1.73 m2). Despite ERT, renal function deteriorated to 60±23 mL/min/1.73 m2 (P=0.04) and left ventricular posterior wall thickness (PWT) did not change (14.0±2.1 vs 13.4±2.3 mm). In contrast, patients without impairment of renal function (n=9) had a more favorable outcome (no clin. events; GFR 115±18 vs 102±14 mL/min/1.73 m2, NS; PWT 11.7±1 and 10.7±0.7 mm, P=0.04). Proteinuria remained unchanged (1.34±0.94 vs 1.01±0.97 g/day, n=10). Patients with impaired renal function have a less favorable outcome and may develop cardiovascular and renal end points despite ERT.

CC 1-12 (Pharmacology)
ST enzyme replacement therapy recombinant alpha galactosidase A fabry disease
IT Fabry disease
Human
(enzyme replacement therapy with r-hαGalA had no effect on left ventricular PWT and proteinuria in fabry disease patient with impaired renal function but those without renal impairment had more favorable outcome)
OS.CITING REF COUNT: 23 THERE ARE 23 CAPLUS RECORDS THAT CITE THIS RECORD (23 CITINGS)
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L152 ANSWER 20 OF 37 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2006:1203707 HCAPLUS Full-text
DOCUMENT NUMBER: 146:226565
TITLE: Fabry disease in mice protects against lethal disease caused by Shiga toxin-expressing enterohemorrhagic Escherichia coli
AUTHOR(S): Cilmi, Salvatore A.; Karalius, Brad J.; Choy, Wendy; Smith, R. Neal; Butterton, Joan R.

CORPORATE SOURCE: Infectious Disease Division, Department of Medicine, Massachusetts General Hospital, Boston, USA
SOURCE: Journal of Infectious Diseases (2006), 194(8), 1135-1140
CODEN: JIDIAQ; ISSN: 0022-1899
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Fabry disease is an X-linked recessive disorder in which affected persons lack α-galactosidase A (α-GalA), which leads to excess glycosphingolipids in tissues, mainly globotriaosylceramide (Gb3). Gb3 is the cellular receptor for Shiga toxin (Stx), the primary virulence factor of enterohemorrhagic Escherichia coli. α-GalA-knockout mice were significantly protected against lethal i.p. doses of Stx2 or oral doses of Stx2-expressing bacteria, compared with wild-type (wt) control mice. Kidneys of moribund wt mice revealed tubular necrosis, but no histopathol. changes were observed in Gb3-overexpressing mice. Reducing Gb3 levels in α-GalA-knockout mice by the i.v. injection of recombinant human α-GalA restored the susceptibility of knockout mice to LDs of Stx2. These results suggest that excess amts. of Gb3 in α-GalA-deficient mice may impair toxin delivery to susceptible tissues.

CC 14-14 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 10

IT Toxins
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(Shiga; α-GalA-knockout Fabry disease mouse model show protection against Stx2 lethal i.p.- /oral dose of Stx2-expressing E. coli and i.v. injection of recombinant human α-GalA lower Gb3, restore Stx2 LD sensitivity)

IT Necrosis
(renal tubular; α-GalA-knockout Fabry disease mouse model show protection against Stx2 lethal i.p.- /oral dose of Stx2-expressing E. coli and i.v. injection of recombinant human α-GalA lower Gb3, restore Stx2 LD sensitivity)

IT Kidney disease
(tubular necrosis; α-GalA-knockout Fabry disease mouse model show protection against Stx2 lethal i.p.- /oral dose of Stx2-expressing E. coli and i.v. injection of recombinant human α-GalA lower Gb3, restore Stx2 LD sensitivity)

IT Escherichia coli
Fabry disease
Human
(α-GalA-knockout Fabry disease mouse model show protection against Stx2 lethal i.p.- /oral dose of Stx2-expressing E. coli and i.v. injection of recombinant human α-GalA lower Gb3, restore Stx2 LD sensitivity)

IT Glycosphingolipids
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(α-GalA-knockout Fabry disease mouse model show protection against Stx2 lethal i.p.- /oral dose of Stx2-expressing E. coli and i.v. injection of recombinant human α-GalA lower Gb3, restore Stx2 LD sensitivity)

IT 9025-35-8, α-Galactosidase A 71965-57-6, Globotriaosylceramide
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)

(α-GalA-knockout Fabry disease mouse model show protection against Stx2 lethal i.p.- /oral dose of Stx2-expressing E. coli and i.v. injection of recombinant human α-GalA lower Gb3, restore Stx2 LD sensitivity)

OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L152 ANSWER 21 OF 37 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2006:381447 HCAPLUS Full-text

DOCUMENT NUMBER: 145:328098

TITLE: Corrective effect on Fabry mice of yeast recombinant human α-galactosidase with N-linked sugar chains suitable for lysosomal delivery

AUTHOR(S): Sakuraba, Hitoshi; Chiba, Yasunori; Kotani, Masaharu; Kawashima, Ikuo; Ohsawa, Mai; Tajima, Youichi; Takaoka, Yuki; Jigami, Yoshifumi; Takahashi, Hiroshi; Hirai, Yukihiko; Shimada, Takashi; Hashimoto, Yasuhiro; Ishii, Kumiko; Kobayashi, Toshihide; Watabe, Kazuhiko; Fukushige, Tomoko; Kanzaki, Tamotsu

CORPORATE SOURCE: Department of Clinical Genetics, The Tokyo Metropolitan Institute of Medical Science, Tokyo Metropolitan Organization for Medical Research, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo, 113-8613, Japan

SOURCE: Journal of Human Genetics (2006), 51(4), 341-352 CODEN: JHGEFR; ISSN: 1434-5161

PUBLISHER: Springer Tokyo

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We have previously reported the production of a recombinant α-galactosidase with engineered N-linked sugar chains facilitating uptake and transport to lysosomes in a Saccharomyces cerevisiae mutant. In this study, we improved the purification procedure, allowing us to obtain a large amount of highly purified enzyme protein with mannose-6-phosphate residues at the non-reducing ends of sugar chains. The products were incorporated into cultured fibroblasts derived from a patient with Fabry disease via mannose-6-phosphate receptors. The ceramide trihexoside (CTH) accumulated in lysosomes was cleaved dose-dependently, and the disappearance of deposited CTH was maintained for at least 7 days after administration. We next examined the effect of the recombinant α-galactosidase on Fabry mice. Repeated intravascular administration of the enzyme led to successful degradation of CTH accumulated in the liver, kidneys, heart, and spleen. However, cleavage of the accumulated CTH in the dorsal root ganglia was insufficient. As the culture of yeast cells is easy and economical, and does not require fetal calf serum, the recombinant α-galactosidase produced in yeast cells is highly promising as an enzyme source for enzyme replacement therapy in Fabry disease.

CC 1-10 (Pharmacology)

ST recombinant alpha galactosidase Saccharomyces Fabry disease enzyme replacement therapy

IT Therapy
RL: BIOL (Biological study); USES (Uses)
(enzyme replacement therapy; recombinant α-galactosidase with N-linked sugar chains from Saccharomyces cerevisiae degraded accumulated ceramide trihexoside in Fabry fibroblast from patient and in different organ of Fabry)

IT Fabry disease
Human

Saccharomyces cerevisiae
(recombinant α-galactosidase with
M6P residues at non-reducing end of N-linked sugar chains from
Saccharomyces cerevisiae degraded accumulated ceramide trihexoside in
Fabry fibroblast from patient and in different organ of Fabry mouse)

IT Heart
(recombinant α-galactosidase with
M6P residues at non-reducing end of N-linked sugar chains from
Saccharomyces cerevisiae degraded accumulated ceramide trihexoside in
heart of Fabry mouse)

IT Kidney
(recombinant α-galactosidase with
M6P residues at non-reducing end of N-linked sugar chains from
Saccharomyces cerevisiae degraded accumulated ceramide trihexoside in
kidney of Fabry mouse)

IT Liver
(recombinant α-galactosidase with
M6P residues at non-reducing end of N-linked sugar chains from
Saccharomyces cerevisiae degraded accumulated ceramide trihexoside in
liver of Fabry mouse)

IT Spleen
(recombinant α-galactosidase with
M6P residues at non-reducing end of N-linked sugar chains from
Saccharomyces cerevisiae degraded accumulated ceramide trihexoside in
spleen of Fabry mouse)

IT Ganglion
(recombinant α-galactosidase with
M6P residues at non-reducing end of N-linked sugar chains from
Saccharomyces cerevisiae did not sufficiently degraded accumulated
ceramide trihexoside dorsal root ganglia of Fabry mouse)

IT Lysosome
(recombinant α-galactosidase with
M6P residues at non-reducing end of N-linked sugar chains from yeast
cell degraded lysosome accumulated ceramide trihexoside in Fabry
fibroblast from patient and in different organ of Fabry mouse)

IT Ceramides
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(trihexosides; recombinant α-
galactosidase with M6P residues at non-reducing end of N-linked
sugar chains from Saccharomyces cerevisiae degraded accumulated
ceramide trihexoside in Fabry fibroblast from patient and in different
organ of Fabry mouse)

IT Glycosphingolipids
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(trihexosylglycosphingolipids; recombinant α-
galactosidase with M6P residues at non-reducing end of N-linked
sugar chains from Saccharomyces cerevisiae degraded accumulated
ceramide trihexoside in Fabry fibroblast from patient and in different
organ of Fabry mouse)

IT 3672-15-9, Mannose-6-phosphate
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(recombinant α-galactosidase with
M6P residues at non-reducing end of N-linked sugar chains from
Saccharomyces cerevisiae degraded accumulated ceramide trihexoside in
Fabry fibroblast from patient and in different organ of Fabry mouse)

IT 9025-35-8
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)

(recombinant α-galactosidase with
M6P residues at non-reducing end of N-linked sugar chains from
Saccharomyces cerevisiae degraded accumulated ceramide trihexoside in
Fabry fibroblast from patient and in different organ of Fabry mouse)

OS.CITING REF COUNT: 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L152 ANSWER 22 OF 37 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2006:678186 HCAPLUS Full-text

DOCUMENT NUMBER: 146:70

TITLE: Fabry disease: clinical spectrum and evidence-based enzyme replacement therapy

AUTHOR(S): Desnick, Robert J.; Banikazemi, Maryam

CORPORATE SOURCE: Department of Human Genetics, Mount Sinai School of Medicine of New York University, New York, NY, 10029, USA

SOURCE: Nephrologie & Therapeutique (2006), 2(Suppl. 2), S172-S185
CODEN: NTEHAD; ISSN: 1769-7255

PUBLISHER: Elsevier SAS

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. The clin. spectrum of Fabry disease, an X-linked lysosomal storage disorder due to α-galactosidase A (α-Gal A) deficiency, has been expanded beyond the classic phenotype to include the recently recognized later-onset "cardiac" and "renal" variants. The clin. manifestations in each of these disease subtypes are presented with particular emphasis on early recognition among pediatric patients as well as identification of unrecognized patients diagnosed as hypertrophic cardiomyopathy or in renal dialysis clinics. Previously, treatment of patients with Fabry disease was limited to palliative care of the excruciating pain, cardiac and cerebrovascular manifestations, and renal failure. Recently, Fabry-specific enzyme replacement therapy (ERT) with recombinant α-Gal A (Fabrazyme) has proven safe and effective. The preclin., Phase 1/2 and multicenter, double-blind, randomized, placebo-controlled Phase 3 and 4 trials provided the evidence for the safety and efficacy of Fabrazyme treatment. The preclin. and Phase 1/2 studies demonstrated that enzyme delivery to various tissues and GL-3 clearance were dose-dependent. The Phase 3 clin. trial and 3-yr extension study provided long-term data documenting the safety and effectiveness of 1 mg/kg of Fabrazyme for this disease. Finally, the "top-line" data from the Phase 4 trial indicates that in patients with mildly to moderately advanced renal disease, Fabrazyme can slow the progression of renal, cardiac, and cerebrovascular events taken together or individually. The Phase 4 trial results also emphasize the importance of early treatment. In sum, these clin. trials provide the evidence-based safety and efficacy of Fabrazyme replacement therapy for Fabry disease.

CC 1-0 (Pharmacology)

IT Fabry disease
Human
(Fabry-specific enzyme replacement therapy with recombinant α-galactosidase A Fabrazyme at dose of 1 mg/kg biweekly is safe and effective in treatment of Fabry disease patients)

IT Therapy
RL: BIOL (Biological study); USES (Uses)
(enzyme therapy; Fabry-specific enzyme replacement therapy with recombinant α-galactosidase A Fabrazyme at dose of 1 mg/kg biweekly is safe and effective in treatment of Fabry disease patients)

IT 9025-35-8, α-Galactosidase A
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Fabry-specific enzyme replacement therapy with recombinant α-galactosidase A Fabrazyme at dose of 1 mg/kg biweekly is safe and effective in treatment of Fabry disease patients)
IT 104138-64-9, Fabrazyme
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Fabry-specific enzyme replacement therapy with recombinant α-galactosidase A Fabrazyme at dose of 1 mg/kg biweekly is safe and effective in treatment of Fabry disease patients)
REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L152 ANSWER 23 OF 37 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2006:331388 HCAPLUS Full-text
DOCUMENT NUMBER: 145:306242
TITLE: The effect of 12-month enzyme replacement therapy on myocardial perfusion in patients with Fabry disease
AUTHOR(S): Kalliokoski, R. J.; Kantola, I.; Kalliokoski, K. K.; Engblom, E.; Sundell, J.; Hannukainen, J. C.; Janatuinen, T.; Raitakari, O. T.; Knuuti, J.; Penttinen, M.; Viikari, J.; Nuutila, P.
CORPORATE SOURCE: Turku PET Centre, University of Turku, Turku, FIN-20521, Finland
SOURCE: Journal of Inherited Metabolic Disease (2006), 29(1), 112-118
CODEN: JIMDDP; ISSN: 0141-8955
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Fabry disease (McKusick 301500) is an X-linked lysosomal storage disorder secondary to deficient α-galactosidase A activity which leads to the widespread accumulation of globotriaosylceramide (Gb3) and related glycosphingolipids, especially in vascular smooth-muscle and endothelial cells. We have recently shown that the myocardial perfusion reserve of Fabry patients is significantly decreased. Thus, in the present study we investigated, whether it can be improved with enzyme replacement therapy (ERT). Ten patients (7 male, 3 female; mean age 34, range 19-49 years) with confirmed Fabry disease were approved for this uncontrolled, open-label study. Myocardial perfusion was measured at rest and during dipyridamole-induced hyperemia by positron emission tomog. and radiowater. Myocardial perfusion reserve was calculated as the ratio between maximal and resting perfusion. Perfusion measurements were performed before and after 6 and 12 mo of ERT by recombinant human α-galactosidase A (Fabrazyme, Genzyme). Plasma Gb3 concentration decreased significantly and the patients reported that they felt better and suffered less pain after the ERT. However, neither resting or dipyridamole-stimulated myocardial perfusion nor myocardial perfusion reserve changed during the ERT. Pretreatment relative wall thickness correlated neg. with posttreatment changes in flow reserve (r = -0.76, p = 0.05) and pos. with posttreatment changes in minimal coronary resistance (r = 0.80, p = 0.03). This study shows that 12 mo of ERT does not improve myocardial perfusion reserve, although the plasma Gb3 concentration decreases. However, individual variation in the response to therapy was large and the results suggest that the success of the therapy may depend on the degree of cardiac hypertrophy.
CC 1-8 (Pharmacology)
IT Fabry disease
Human
(enzyme replacement therapy with recombinant human

α-galactosidase A of 12-mo decreased plasma
globotriaosylceramide but not improved dipyridamole-stimulated
myocardial blood flow and flow reserve in Fabry disease patient)

IT Circulation
Heart
Perfusion
(enzyme replacement therapy with recombinant human
α-galactosidase A of 12-mo did not improved
dipyridamole-stimulated myocardial blood flow and flow reserve in Fabry
disease patient)

IT Therapy
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(enzyme replacement therapy; enzyme replacement therapy with
recombinant human α-
galactosidase A of 12-mo decreased plasma globotriaosylceramide
but not improved dipyridamole-stimulated myocardial blood flow and flow
reserve in Fabry disease patient)

IT 58-32-2, Dipyridamole
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(enzyme replacement therapy with recombinant human
α-galactosidase A of 12-mo decreased plasma
globotriaosylceramide but not improved dipyridamole-stimulated
myocardial blood flow and flow reserve in Fabry disease patient)

IT 104138-64-9, Fabrazyme
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(enzyme replacement therapy with recombinant human
α-galactosidase A of 12-mo decreased plasma
globotriaosylceramide but not improved dipyridamole-stimulated
myocardial blood flow and flow reserve in Fabry disease patient)

IT 71965-57-6, Globotriaosylceramide
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(enzyme replacement therapy with recombinant human
α-galactosidase A of 12-mo decreased plasma
globotriaosylceramide in Fabry disease patient)

OS.CITING REF COUNT: 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L152 ANSWER 24 OF 37 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2005:119337 HCAPLUS Full-text
DOCUMENT NUMBER: 143:264872
TITLE: Monitoring enzyme replacement therapy in Fabry disease-Role of urine globotriaosylceramide
AUTHOR(S): Whitfield, P. D.; Calvin, J.; Hogg, S.; O'Driscoll, E.; Halsall, D.; Burling, K.; Maguire, G.; Wright, N.; Cox, T. M.; Meikle, P. J.; Deegan, P. B.
CORPORATE SOURCE: Biochemical Genetics Unit, Addenbrooke's NHS Trust, Cambridge, UK
SOURCE: Journal of Inherited Metabolic Disease (2005), 28(1), 21-33
CODEN: JIMDDP; ISSN: 0141-8955
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Anderson-Fabry disease (referred to as Fabry disease) is an X-linked disorder characterized by a deficiency of the lysosomal enzyme α-galactosidase A and

the subsequent accumulation in various tissues of globotriaosylceramide (Gb3), the main substrate of the defective enzyme. Enzyme replacement therapy (ERT) offers a specific treatment for patients with Fabry disease, though monitoring of treatment is hampered by a lack of surrogate markers of response. In this study, the efficacy of long-term ERT in six Fabry hemizygotes and two symptomatic heterozygotes has been evaluated. Patients were administered recombinant α-galactosidase A every 2 wk for up to a year. The efficacy of ERT was assessed by monitoring symptomatol. and renal function. Urinary glycolipid concentration was estimated by a novel tandem mass spectrometric method. Urine glycolipid (Gb3) was elevated at baseline and fell impressively on ERT where patients were hemizygotes and in the absence of renal transplantation. In heterozygotes and in a recipient of a renal allograft, elevations and changes in urine glycolipids were less pronounced. In one patient, after several months of ERT, there was a transient increase in Gb3 concns. to baseline (pre-ERT) levels, associated with the presence of antibodies to the recombinant α-galactosidase A. The marked decline in urine Gb3 on ERT, and its subsequent increase in association with an inhibitory antibody response, suggest that this analyte deserves further investigation as a potential marker of disease severity and response to treatment.

CC 14-14 (Mammalian Pathological Biochemistry)

IT Fabry disease
(enzyme replacement therapy led to immunol. consequences, impaired efficacy in Anderson-Fabry disease patient and urinary globotriaosylceramide lowered initially but increased with inhibitory antibody response suggesting it as biomarker)

IT Human
Prognosis
(enzyme replacement therapy led to immunol. consequences, impaired efficacy in Fabry disease patient and urinary globotriaosylceramide declined initially but increased with inhibitory antibody response suggesting it as biomarker)

IT Therapy
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enzyme replacement therapy; ERT with recombinant α-galactosidase A led to immunol. consequences, impaired efficacy in Fabry disease patient and urinary globotriaosylceramide lowered initially but raised with inhibitory antibody response implying it as biomarker)

IT 9025-35-8, α-Galactosidase A
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ERT with recombinant α-galactosidase A led to immunol. consequences, impaired efficacy in Fabry disease patient and urinary globotriaosylceramide lowered initially but raised with inhibitory antibody response implying it as biomarker)

OS.CITING REF COUNT: 21 THERE ARE 21 CAPLUS RECORDS THAT CITE THIS RECORD (21 CITINGS)
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L152 ANSWER 25 OF 37 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2003:26826 HCAPLUS Full-text
DOCUMENT NUMBER: 139:686
TITLE: Recombinant enzyme therapy for fabry disease: absence of editing of human .alpha.-galactosidase A mRNA
AUTHOR(S): Blom, Daniel; Speijer, Dave; Linthorst, Gabor E.; Donker-Koopman, Wilma G.; Strijland, Anneke; Aerts,

Johannes M. F. G.
CORPORATE SOURCE: Department of Biochemistry, Academic Medical Centre, University of Amsterdam, Amsterdam, 1105 AZ, Neth.
SOURCE: American Journal of Human Genetics (2003), 72(1), 23-31
CODEN: AJHGAG; ISSN: 0002-9297
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB For more than a decade, protein-replacement therapy has been employed successfully for the treatment of Gaucher disease. Recently, a comparable therapy has become available for the related lipid-storage disorder Fabry disease. Two differently produced recombinant α-galactosidase A (α-gal A) prepns. are used independently for this purpose. Agalsidase α is obtained from human fibroblasts that have been modified by gene activation; agalsidase β is obtained from Chinese hamster ovary cells that are transduced with human α-gal A cDNA. It has previously been claimed that α-gal A mRNA undergoes editing, which may result in coprodn. of an edited protein (Phe 396 Tyr) that might have a relevant physiol. function. We therefore analyzed the occurrence of α-gal A editing, as well as the precise nature, in this respect, of the therapeutic enzymes. No indications were obtained for the existence of editing at the protein or RNA level. Both recombinant enzymes used in therapy are unedited and are capable of functionally correcting cultured fibroblasts from Fabry patients in their excessive globotriaosylceramide accumulation. Although RNA editing is apparently not relevant in the case of α-gal A, a thorough anal. of the potential occurrence of editing of transcripts is nevertheless advisable in connection with newly developed protein-replacement therapies.

CC 1-10 (Pharmacology)

IT mRNA
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(for α-galactosidase A; recombinant α-galactosidase A enzyme replacement therapy for Fabry disease)

IT Fabry disease
Human
RNA editing
(recombinant α-galactosidase A enzyme replacement therapy for Fabry disease)

IT 9025-35-8, α-Galactosidase A
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(recombinant α-galactosidase A enzyme replacement therapy for Fabry disease)

OS.CITING REF COUNT: 19 THERE ARE 19 CAPLUS RECORDS THAT CITE THIS RECORD (19 CITINGS)
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L152 ANSWER 26 OF 37 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2002:748740 HCAPLUS Full-text
DOCUMENT NUMBER: 137:275012
TITLE: Purification of recombinant .alpha.-galactosidase A and its glycosylation modification for treatment of Fabry disease and related therapy by targeted gene activation
INVENTOR(S): Selden, Richard F.; Borowski, Marianne; Kinoshita, Carol M.; Treco, Douglas A.; Williams, Melanie D.; Schuetz, Thomas J.; Daniel, Peter F.

PATENT ASSIGNEE(S): Transkaryotic Therapies, Inc., USA
SOURCE: U.S., 39 pp., Cont.-in-part of U. S. Ser. No. 928,881. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6458574	B1	20021001	US 1999-266014	19990311
WO 9811206	A2	19980319	WO 1997-US16603	19970912
WO 9811206	A3	19980813		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 6083725	A	20000704	US 1997-928881	19970912
CA 2365923	A1	20000914	CA 2000-2365923	20000309
WO 2000053730	A2	20000914	WO 2000-US6118	20000309
WO 2000053730	A3	20010315		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
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AU 2000035194	A	20000928	AU 2000-35194	20000309
EP 1163349	A2	20011219	EP 2000-913825	20000309
EP 1163349	B1	20080220		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY				
CN 1354796	A	20020619	CN 2000-807312	20000309
CN 100417727	C	20080910		
HU 2002000467	A2	20020629	HU 2002-467	20000309
HU 2002000467	A3	20060628		
JP 2002538183	T	20021112	JP 2000-603353	20000309
NZ 514077	A	20040227	NZ 2000-514077	20000309
RU 2248213	C2	20050320	RU 2001-127533	20000309
EP 1820862	A2	20070822	EP 2006-25159	20000309
EP 1820862	A3	20071031		
R: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
AT 386808	T	20080315	AT 2000-913825	20000309
PT 1163349	E	20080519	PT 2000-913825	20000309
ES 2300256	T3	20080616	ES 2000-913825	20000309
CN 101219213	A	20080716	CN 2007-10148292	20000309
IL 145381	A	20091224	IL 2000-145381	20000309
EP 2186902	A2	20100519	EP 2010-152432	20000309
R: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
NO 2001004415	A	20011112	NO 2001-4415	20010911
MX 2001009222	A	20020604	MX 2001-9222	20010911
KR 892334	B1	20090408	KR 2001-711552	20010911

AU 762400	B2	20030626	AU 2001-93403	20011123
US 20030077806	A1	20030424	US 2002-165060	20020607
US 20030113894	A1	20030619	US 2002-165968	20020610
HK 1043386	A1	20080613	HK 2002-104366	20020611
AU 2003220717	A1	20030814	AU 2003-220717	20030722
AU 2003220717	B2	20071018		
AU 2004242550	A1	20050127	AU 2004-242550	20041231
AU 2004242550	B2	20080403		
KR 2007090277	A	20070905	KR 2007-719031	20070820
KR 961740	B1	20100607		
AU 2008200265	A1	20080207	AU 2008-200265	20080118
AU 2008202567	A1	20080703	AU 2008-202567	20080611

PRIORITY APPLN. INFO.:

US 1996-26041P	P	19960913
US 1997-928881	A2	19970912
WO 1997-US16603	A2	19970912
US 1996-712614	A	19960913
AU 1997-44244	A3	19970912
US 1999-266014	A	19990311
AU 2000-35194	A3	20000309
CN 2000-807312	A3	20000309
EP 2000-913825	A3	20000309
EP 2006-25159	A3	20000309
WO 2000-US6118	W	20000309
KR 2001-711552	A3	20010911
AU 2003-220717	A3	20030722
AU 2004-242550	A3	20041231

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The invention provides highly purified α-Gal A, and various methods for purifying it; α-Gal A prepns. with altered charge and methods for making those prepns.; α-Gal A prepns. that have an extended circulating half-life in a mammalian host, and methods for making same; and methods and dosages for administering an α-Gal A preparation to a subject. Several α-Gal A expression vectors are constructed to improve its recombinant expression in foreskin fibroblast cell. The recombinant enzyme is purified to >98% homogeneity and in 59% yield, and with a specific activity of 2.92 X 106 units/mg protein using Bu Sepharose, Heparin Sepharose, hydroxyapatite, Q Sepharose, and Superdex 200 column chromatog. The purified enzyme are further subjected to glycosylation modification by neuraminidase (or sialidase) treatment and then fractionated by size and charge for the enrichment of highly charged glycoforms of α-Gal A. To improve drug uptake for Fabry disease treatment, the purified enzyme are desialylated and degalactosylated and tested for the biodistribution after injected into the mice. Desialylated α-Gal A localized more to the liver than did the untreated enzyme. Another vector pGA213C is also provided for targeted gene correction and activation. Fabry fibroblast cocultured with recombinant fibroblast secreting α-Gal A internalized the enzyme and exhibited α-Gal A activity similar to that of normal cells.

IC ICM C12N009-40
ICS A61K038-43

INCL 435208000

CC 7-2 (Enzymes)
Section cross-reference(s): 1, 3, 14, 63

IT Functional groups
(carbohydrate groups of α galactosidase, PEG conjugated to; purification of recombinant α-galactosidase A and glycosylation modification for treatment of Fabry disease and related therapy by targeted gene activation)

IT Polyoxyalkylenes, biological studies
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES

(Uses)
(conjugated to α galactosidase for uptake improvement; purification of recombinant α-galactosidase A and glycosylation modification for treatment of Fabry disease and related therapy by targeted gene activation)

IT Fibroblast
(foreskin, recombinant α galactosidase secreting; purification of recombinant α-galactosidase A and glycosylation modification for treatment of Fabry disease and related therapy by targeted gene activation)

IT Fabry disease
(gene or enzyme treatment of; purification of recombinant α-galactosidase A and glycosylation modification for treatment of Fabry disease and related therapy by targeted gene activation)

IT Post-translational processing
(glycosylation or phosphorylation; purification of recombinant α-galactosidase A and glycosylation modification for treatment of Fabry disease and related therapy by targeted gene activation)

IT Liver
(injected α galactosidase uptaken by; purification of recombinant α-galactosidase A and glycosylation modification for treatment of Fabry disease and related therapy by targeted gene activation)

IT Glycosylation
(modification of purified α galactosidase; purification of recombinant α-galactosidase A and glycosylation modification for treatment of Fabry disease and related therapy by targeted gene activation)

IT Promoter (genetic element)
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(of cytomegalovirus, insertion upstream of galactosidase gene of; purification of recombinant α-galactosidase A and glycosylation modification for treatment of Fabry disease and related therapy by targeted gene activation)

IT Amino group
Carboxyl group
Sulfhydryl group
(of α galactosidase, PEG conjugated to; purification of recombinant α-galactosidase A and glycosylation modification for treatment of Fabry disease and related therapy by targeted gene activation)

IT Plasmid vectors
(pGA213C, for activation of galactosidase gene expression; purification of recombinant α-galactosidase A and glycosylation modification for treatment of Fabry disease and related therapy by targeted gene activation)

IT Plasmid vectors
(pXAG-16, α galactosidase expression vector; purification of recombinant α-galactosidase A and glycosylation modification for treatment of Fabry disease and related therapy by targeted gene activation)

IT Plasmid vectors
(pXAG-28, α galactosidase expression vector; purification of

recombinant α-galactosidase A and
glycosylation modification for treatment of Fabry disease and related
therapy by targeted gene activation)

IT Phosphorylation, biological
(protein, modification of; purification of recombinant
α-galactosidase A and glycosylation
modification for treatment of Fabry disease and related therapy by
targeted gene activation)

IT Gene therapy
Human
Molecular cloning
(purification of recombinant α-
galactosidase A and glycosylation modification for treatment of
Fabry disease and related therapy by targeted gene activation)

IT Mus
(testing the uptake of injected α galactosidase; purification of
recombinant α-galactosidase A and
glycosylation modification for treatment of Fabry disease and related
therapy by targeted gene activation)

IT 116874-53-4, Sepharose Q 157885-28-4, Butyl Sepharose 4FF 255732-76-4,
Sepharose 6 Fast Flow Heparin
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES
(Uses)
(chromatog. using; purification of recombinant α-
galactosidase A and glycosylation modification for treatment of
Fabry disease and related therapy by targeted gene activation)

IT 25322-68-3, PEG
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES
(Uses)
(conjugated to α galactosidase for uptake improvement; purification of
recombinant α-galactosidase A and
glycosylation modification for treatment of Fabry disease and related
therapy by targeted gene activation)

IT 83744-93-8, Acetylglucosaminyltransferase, uridine
diphosphoacetylglucosamine-β-1,4-mannosylglycoprotein β-1,4-N-
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES
(Uses)
(modification of galactosidase glycosylation with; purification of
recombinant α-galactosidase A and
glycosylation modification for treatment of Fabry disease and related
therapy by targeted gene activation)

IT 9001-67-6, Sialidase 9031-11-2, β-Galactosidase 9075-81-4
RL: BUU (Biological use, unclassified); CAT (Catalyst use); BIOL
(Biological study); USES (Uses)
(modification of galactosidase glycosylation with; purification of
recombinant α-galactosidase A and
glycosylation modification for treatment of Fabry disease and related
therapy by targeted gene activation)

IT 9026-43-1
RL: BUU (Biological use, unclassified); CAT (Catalyst use); BIOL
(Biological study); USES (Uses)
(modification of galactosidase phosphorylation with; purification of
recombinant α-galactosidase A and
glycosylation modification for treatment of Fabry disease and related
therapy by targeted gene activation)

IT 1306-06-5, Hydroxyapatite 201491-03-4, Superdex-200
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES
(Uses)

(purification of recombinant α-galactosidase A and glycosylation modification for treatment of Fabry disease and related therapy by targeted gene activation)

IT 9025-35-8P, α-Galactosidase A
RL: PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(purification of recombinant α-galactosidase A and glycosylation modification for treatment of Fabry disease and related therapy by targeted gene activation)

IT 464240-34-4, 1: PN: US6458574 SEQID: 1 unclaimed DNA 464240-35-5, 2: PN: US6458574 SEQID: 2 unclaimed DNA 464240-36-6, 3: PN: US6458574 SEQID: 3 unclaimed DNA 464240-38-8, 5: PN: US6458574 SEQID: 5 unclaimed DNA
464240-39-9 464240-40-2 464240-41-3 464240-42-4 464240-43-5
464240-44-6 464240-45-7 464240-46-8 464240-47-9 464240-48-0
464240-49-1 464240-50-4 464240-51-5 464240-52-6 464240-53-7
464240-54-8 464240-55-9 464240-56-0 464240-57-1
RL: PRP (Properties)
(unclaimed nucleotide sequence; purification of recombinant α-galactosidase A and its glycosylation modification for treatment of Fabry disease and related therapy by targeted gene activation)

IT 464240-37-7
RL: PRP (Properties)
(unclaimed protein sequence; purification of recombinant α-galactosidase A and its glycosylation modification for treatment of Fabry disease and related therapy by targeted gene activation)

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L152 ANSWER 27 OF 37 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2002:746445 HCAPLUS Full-text
DOCUMENT NUMBER: 138:164074
TITLE: Production of glycoprotein for enzyme replacement therapy of Fabry disease in yeast
AUTHOR(S): Chiba, Yasunori; Sakuraba, Hitoshi; Jigami, Yoshifumi
CORPORATE SOURCE: Institute of Molecular and Cell Biology, National Institute of Advanced Industrial Science and Technology, Japan
SOURCE: Jikken Igaku (2002), 20(12), 1823-1827
CODEN: JIIGEF; ISSN: 0288-5514
PUBLISHER: Yodosha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review on the genetic engineering of Saccharomyces cerevisiae mutant (OCH1 and MNN1 gene deficiency) that will produce glycoprotein with human M6P type sugar chain, and recombinant manufacture of α-galactosidase with the S. cerevisiae mutant for the enzyme replacement therapy of Fabry disease, a genetic disease associated with the X chromosome.

CC 3-0 (Biochemical Genetics)
Section cross-reference(s): 1, 16

IT Fabry disease
Fermentation
Human
Saccharomyces cerevisiae
(recombinant production of glycoprotein with yeast for enzyme replacement therapy of Fabry disease)

IT 9025-35-8P, α-Galactosidase
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(recombinant production of glycoprotein with yeast for enzyme replacement therapy of Fabry disease)

L152 ANSWER 28 OF 37 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2002:567114 HCAPLUS Full-text
DOCUMENT NUMBER: 137:214716
TITLE: Fabry disease: 45 novel mutations in the α-galactosidase A gene causing the classical phenotype
AUTHOR(S): Shabbeer, Junaid; Yasuda, Makiko; Luca, Edlira; Desnick, Robert J.
CORPORATE SOURCE: Department of Human Genetics, Mount Sinai School of Medicine, New York, NY, 10029, USA
SOURCE: Molecular Genetics and Metabolism (2002), 76(1), 23-30
CODEN: MGMEFF; ISSN: 1096-7192
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The nature of the mol. lesions in the α-galactosidase A (α-Gal A) gene causing Fabry disease was determined in 50 unrelated families with the classic phenotype of this X-linked recessive lysosomal storage disease. Genomic DNA was isolated from affected males or obligate carrier females, and the entire α-Gal A coding region as well as the flanking and intronic sequences were analyzed by PCR amplification and automated sequencing. Forty-five new mutations were identified including 38 single base substitutions (32 missense and four nonsense) and nine gene rearrangements: MIR, M42T, G43D, G43V, H46Y, F50C, L68F, G132R, T141I, Y152X, K168R, G183S, V199M, P205R, Y207S, Q221X, C223R, C223Y, D234Y, G271C, A288P, P293A, R301G, I303N, I317T, E341D, P362L, R363C, R363H, G373D, I384N, T385P, Q396X, E398K, S401X, P409A, g7325insC, g7384del13, g8341delG, g8391del4/ins3, g10511delTAGT, g10704delACAG, g11019insG, g11021insG, and g11048delAGG. In the remaining five Fabry families, four previously reported mutations were detected (W81X, R112C, g11011delTC, and g11050delGAG) of which the R112C substitution was found in two families who were unrelated by haplotyping. These studies further define the heterogeneity of mutations in the α-Gal A gene causing the classical Fabry disease phenotype, and permit precise carrier detection and prenatal diagnosis in these families.

CC 14-1 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 3

IT Human
Phenotypes
(45 novel mutations in α-galactosidase A gene causing classical phenotype of human Fabry disease)

IT Lysosomal storage disease
(X-linked recessive; 45 novel mutations in α-galactosidase A gene causing classical phenotype of human Fabry disease)

IT Fabry disease
(human; 45 novel mutations in α-galactosidase A gene causing classical phenotype of human Fabry disease)

IT Mutation
(insertion; 45 novel mutations in α-galactosidase A gene causing classical phenotype of human Fabry disease)

IT Mutation
(missense; 45 novel mutations in α-galactosidase A gene causing classical phenotype of human Fabry disease)

IT Mutation
(nonsense; 45 novel mutations in α-galactosidase A gene causing classical phenotype of human Fabry disease)
IT Heterogeneity
(of α-Gal A gene mutation; 45 novel mutations in α-galactosidase A gene causing classical phenotype of human Fabry disease)
IT Diagnosis
(prenatal; 45 novel mutations in α-galactosidase A gene causing classical phenotype of human Fabry disease)
IT Recombination, genetic
(rearrangement; 45 novel mutations in α-galactosidase A gene causing classical phenotype of human Fabry disease)
IT Mutation
(substitution; 45 novel mutations in α-galactosidase A gene causing classical phenotype of human Fabry disease)
IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(α-Gal A; 45 novel mutations in α-galactosidase A gene causing classical phenotype of human Fabry disease)
IT 9025-35-8, α-Galactosidase A
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(45 novel mutations in α-galactosidase A gene causing classical phenotype of human Fabry disease)

OS.CITING REF COUNT: 13 THERE ARE 13 CAPLUS RECORDS THAT CITE THIS RECORD (13 CITINGS)
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L152 ANSWER 29 OF 37 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2001:536104 HCAPLUS Full-text
DOCUMENT NUMBER: 135:298605
TITLE: Safety and efficacy of recombinant human α-galactosidase A replacement therapy in Fabry's disease
AUTHOR(S): Eng, Christine M.; Guffon, Nathalie; Wilcox, William R.; Germain, Dominique P.; Lee, Philip; Waldek, Steve; Caplan, Louis; Linthorst, Gabor E.; Desnick, Robert J.; Banikazemi, M.; Ibraham, J.; Cheng, A. P.; Raffel, L. J.; Cochat, P.; Azizi, M.; Jeunemaitre, X.; Vellodi, A.; Wraith, J. E.; Chaves, C. J.; Kanis, K. B.; Linfante, I.; Llinas, R.; Bosman, D. K.; Heymans, H. S. A.; Hollak, C. E. M.; Wijburg, F. A.; Colvin, R. B.; Dikman, S.; Rennke, H.; Aretz, H. T.; Fallon, J.; Mitchell, R.; Beyers, H. R.; Grenler, S.; Phelps, R.; Gordon, R. E.; Brodie, S.; Gass, S. A.; Goldman, M.; Mehra, D.; Winston, J.; Bouvier, R.; Denis, B. P.; Dubourg, L.; Fouilhoux, A.; Hadj-Aissa, A.; Laville, M.; Maire, I.; Ranchin, B.; Vanier, M. T.; Hickey, A.; Jordan, J.; Jordan, S.; Khan, S. S.; Maguen, E.; Amrein, C.; Diebold, B.; fiessinger, J. N.; Froissart, M.; Grunfeld, J. P.; Julien, J.; Noel, L. H.; Orssaud, C.; Poenaru, L.; Griffiths, M. H.; Holdright, D.; Phelps-brown, N.; Sporton, S.; Woolfson, R.; Worthington, V. C.; Young, E. P.; Bhushan, M.; Cooper,

A.; O'Rioridan, E.; Radford, R.; Ray, S. G.; Reeve, R. S.; Berson, F. G.; Kruskall, M. S.; Manning, W. J.; Bos, W. J. W.; Bosman, D. K.; ten Kate, F. J. W.; Krediet, R. T.; Lie, K. I.; Piek, J. J.; Prick, L. J. J. M.; Smitt, J. H. S.; Nunn, M.; Nieto, A.; Denchy, R. A.; Kowalski, A.; Exantus, J.; Dupret, M. T.; Garnier, S.; Walbilic, S.; Verne, A. G.; Williams, B.; Bernard, M. C.; Remones, V.; Morrison, J.; Burke, D. G.; Fulford, L. G.; Jackson, M.; Lobo, R.; Sporton, S.; Worthington, V. C.; Kenny, B. M.; Baron, L.; Vyth, A.; Moscicki, R.; Braakman, T.; Goldberg, M.; O'Callaghan, M.; Cintron, R.; Richards, S.; Tandon, P. K.; Fitzpatrick, M. A.; Yelmene, M.; Nichols, M.

CORPORATE SOURCE: International Collaborative Fabry Disease Study Group, Mount Sinai School of Medicine, New York, NY, 10029, USA

SOURCE: New England Journal of Medicine (2001), 345(1), 9-16
CODEN: NEJMAG; ISSN: 0028-4793

PUBLISHER: Massachusetts Medical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background Fabry's disease, lysosomal α-galactosidase A deficiency, results from the progressive accumulation of globotriaosylceramide and related glycosphingolipids. Affected patients have microvascular disease of the kidneys, heart, and brain. Methods We evaluated the safety and effectiveness of recombinant α-galactosidase A in a multicenter, randomized, placebo-controlled, double-blind study of 58 patients who were treated every 2 wk for 20 wk. Thereafter, all patients received recombinant α-galactosidase A in an open-label extension study. The primary efficacy end point was the percentage of patients in whom renal microvascular endothelial deposits of globotriaosylceramide were cleared (reduced to normal or near-normal levels). We also evaluated the histol. clearance of microvascular endothelial deposits of globotriaosylceramide in the endomyocardium and skin, as well as changes in the level of pain and the quality of life. Results In the double-blind study, 20 of the 29 patients in the recombinant α-galactosidase A group (69 %) had no microvascular endothelial deposits of globotriaosylceramide after 20 wk, as compared with none of the 29 patients in the placebo group (P<0.001). Patients in the recombinant α-galactosidase A group also had decreased microvascular endothelial deposits of globotriaosylceramide in the skin (P<0.001) and heart (P<0.001). Plasma levels of globotriaosylceramide were directly correlated with clearance of the microvascular deposits. After six months of open-label therapy, all patients in the former placebo group and 98 % of patients in the former recombinant α-galactosidase A group who had biopsies had clearance of microvascular endothelial deposits of globotriaosylceramide. Mild-to-moderate infusion reactions (i.e., rigors and fever) were more common in the recombinant α-galactosidase A group than in the placebo group. Conclusions Recombinant α-galactosidase A replacement therapy cleared microvascular endothelial deposits of globotriaosylceramide from the kidneys, heart, and skin in patients with Fabry's disease, reversing the pathogenesis of the chief clin. manifestations of this disease.

CC 1-10 (Pharmacology)

IT Blood vessel
(microvessel, endothelium; recombinant α-galactosidase A replacement therapy clears microvascular endothelial deposits of globotriaosylceramide from the kidneys, heart, and skin in humans with Fabry's disease)

IT Heart
Kidney
Skin

(recombinant α-galactosidase A
replacement therapy clears microvascular endothelial deposits of
globotriaosylceramide from the kidneys, heart, and skin in humans with
Fabry's disease)
IT Fabry disease
(safety and efficacy of recombinant human
α-galactosidase A replacement therapy in
Fabry's disease)
IT 71965-57-6, Globotriaosylceramide
RL: ADV (Adverse effect, including toxicity); BPR (Biological process);
BSU (Biological study, unclassified); BIOL (Biological study); PROC
(Process)
(recombinant α-galactosidase A
replacement therapy clears microvascular endothelial deposits of
globotriaosylceramide from the kidneys, heart, and skin in humans with
Fabry's disease)
IT 9025-35-8, α-Galactosidase A
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(safety and efficacy of recombinant human
α-galactosidase A replacement therapy in
Fabry's disease)
OS.CITING REF COUNT: 301 THERE ARE 301 CAPLUS RECORDS THAT CITE THIS RECORD (301 CITINGS)
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L152 ANSWER 30 OF 37 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2000:818937 HCAPLUS Full-text
DOCUMENT NUMBER: 134:146439
TITLE: Expression and Characterization of Glycosylated and Catalytically Active Recombinant Human α-Galactosidase A Produced in Pichia pastoris
AUTHOR(S): Chen, Yingsi; Jin, Ming; Egborge, Tobore; Coppola, George; Andre, Jamie; Calhoun, David H.
CORPORATE SOURCE: Department of Chemistry, City College of New York, New York, NY, 10031, USA
SOURCE: Protein Expression and Purification (2000), 20, 472-484
CODEN: PEXPEJ; ISSN: 1046-5928
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Fabry disease is an X-linked inborn error of glycolipid metabolism caused by deficiency of the lysosomal enzyme α-galactosidase A. This enzyme is responsible for the hydrolysis of terminal α-galactoside linkages in various glycolipids. An improved method of production of recombinant α-galactosidase A for use in humans is needed in order to develop new approaches for enzyme therapy. Human α-galactosidase A for use in enzyme therapy has previously been obtained from human sources and from recombinant clones derived from human cells, CHO cells, and insect cells. In this report we describe the construction of clones of the methylotrophic yeast Pichia pastoris that produce recombinant human α-galactosidase A. Recombinant human α-galactosidase A is secreted by these Pichia clones and the level of production is more than 30-fold greater than that of previously used methods. Production was optimized using variations in temperature, pH, cDNA copy number, and other

variables using shake flasks and a bioreactor. Expression of the human enzyme increased with increasing cDNA copy number at 25°C, but not at the standard growth temperature of 30°C. The recombinant α-galactosidase A was purified to homogeneity using ion exchange (POROS 20 CM, POROS 20 HQ) and hydrophobic (Toso-ether, Toso-butyl) chromatog. with a BioCAD HPLC Workstation. Purified recombinant α-galactosidase A was taken up by fibroblasts derived from Fabry disease patients and normal enzyme levels could be restored under these conditions. Anal. of the carbohydrate present on the recombinant enzyme indicated the predominant presence of N-linked high-mannose structures rather than complex carbohydrates. (c) 2000 Academic Press.

CC 16-2 (Fermentation and Bioindustrial Chemistry)
Section cross-reference(s): 3, 14

ST Pichia recombinant human alpha glucosidase prodn

IT Glycosylation
(biol.; glycosylated recombinant human α-galactosidase A produced in Pichia pastoris)

IT Fermentation
(fed-batch; glycosylated recombinant human α-galactosidase A produced in Pichia pastoris)

IT Fabry disease
Gene dosage
Genetic engineering
Hydrophobic interaction chromatography
Ion exchange chromatography
Komagataella pastoris
Temperature effects, biological
pH
(glycosylated recombinant human α-galactosidase A produced in Pichia pastoris)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(human α-glucosidase; glycosylated recombinant human α-galactosidase A produced in Pichia pastoris)

IT Signal peptides
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(yeast α-mating factor; glycosylated recombinant human α-galactosidase A produced in Pichia pastoris)

IT 9001-42-7P, α-Glucosidase
RL: BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(glycosylated recombinant human α-galactosidase A produced in Pichia pastoris)

IT 56-81-5, Glycerol, biological studies 67-56-1, Methanol, biological studies 7782-44-7, Oxygen, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(glycosylated recombinant human α-galactosidase A produced in Pichia pastoris)

IT 9001-42-7D, α-Glucosidase, fusion protein with yeast α mating factor signal peptide
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)

(glycosylated recombinant human α-
galactosidase A produced in Pichia pastoris)
OS.CITING REF COUNT: 21 THERE ARE 21 CAPLUS RECORDS THAT CITE THIS RECORD (22 CITINGS)
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L152 ANSWER 31 OF 37 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2000:47077 HCAPLUS Full-text
DOCUMENT NUMBER: 132:303452
TITLE: Enzymatic corrections for cells derived from Fabry disease patients by a recombinant adenovirus vector
AUTHOR(S): Ohsugi, Keiko; Kobayashi, Keiko; Itoh, Kohji; Sakuraba, Hitoshi; Sakuragawa, Norio
CORPORATE SOURCE: Department of Inherited Metabolic Disease, National Center of Neurology and Psychiatry, National Institute of Neuroscience, Tokyo, 187-8502, Japan
SOURCE: Journal of Human Genetics (2000), 45(1), 1-5
CODEN: JHGEFR; ISSN: 1434-5161
PUBLISHER: Springer-Verlag Tokyo
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Fabry disease is an X-linked inherited metabolic disorder caused by a deficiency of α-galactosidase (α-gal), resulting in the accumulation of ceramide trihexoside (CTH) in body fluids and in many organs and tissues. The authors constructed a recombinant adenovirus with a human α-gal cDNA (AxCAG α-gal), and transfected this vector to skin fibroblasts from Fabry patients. Transfected cells expressed high amts. of α-gal in their cytoplasm, and a high level of α-gal activity was detected in the medium. The accumulated CTH in the fibroblasts disappeared 3 days after infection. The secreted α-gal also eliminated the accumulated CTH from uninfected patient's cells. The enzyme may be taken up through mannose-6-phosphate receptors, as the addition of mannose-6-phosphate to the medium completely inhibited the uptake of the enzyme. The infected cells continued to express α-gal for more than 10 days. These results suggest that AxCAG α-gal could be used as enzyme replacement gene therapy for Fabry disease.
CC 1-12 (Pharmacology)
Section cross-reference(s): 3
IT Gene
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(GLA; enzymic corrections for skin fibroblasts derived from Fabry disease patients by a recombinant adenovirus vector with a human α-galactosidase cDNA)
IT Human adenovirus
(as viral vector; enzymic corrections for skin fibroblasts derived from Fabry disease patients by a recombinant adenovirus vector with a human α-galactosidase cDNA)
IT Cytoplasm
Fabry disease
Fibroblast
Gene therapy
Skin
Virus vectors
(enzymic corrections for skin fibroblasts derived from Fabry disease patients by a recombinant adenovirus vector with a human α-galactosidase cDNA)
IT cDNA

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enzymic corrections for skin fibroblasts derived from Fabry disease patients by a recombinant adenovirus vector with a human α-galactosidase cDNA)

IT Insulin-like growth factor II receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(enzymic corrections for skin fibroblasts derived from Fabry disease patients by a recombinant adenovirus vector with a human α-galactosidase cDNA)

IT Biological transport
(uptake; enzymic corrections for skin fibroblasts derived from Fabry disease patients by a recombinant adenovirus vector with a human α-galactosidase cDNA)

IT 71965-57-6, Ceramide trihexoside
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(enzymic corrections for skin fibroblasts derived from Fabry disease patients by a recombinant adenovirus vector with a human α-galactosidase cDNA)

IT 9025-35-8, E.C. 3.2.1.22
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene; enzymic corrections for skin fibroblasts derived from Fabry disease patients by a recombinant adenovirus vector with a human α-galactosidase cDNA)

OS.CITING REF COUNT: 9 THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L152 ANSWER 32 OF 37 BIOTECHNO COPYRIGHT 2010 Elsevier Science B.V. on STN DUPLICATE

ACCESSION NUMBER: 2003:36592316 BIOTECHNO Full-text

TITLE: A biochemical and pharmacological comparison of enzyme replacement therapies for the glycolipid storage disorder Fabry disease

AUTHOR: Lee K.; Jin X.; Zhang K.; Copertino L.; Andrews L.; Baker-Malcolm J.; Geagan L.; Qiu H.; Seiger K.; Barngrover D.; McPherson J.M.; Edmunds T.

CORPORATE SOURCE: T. Edmunds, Cell and Protein Therapeutics, Genzyme Corporation, P.O. Box 9322, Framingham, MA 01701-9322, United States.
E-mail: tim.edmunds@genzyme.com

SOURCE: Glycobiology, (01 APR 2003), 13/4 (305-313), 22 reference(s)
CODEN: GLYCE3 ISSN: 0959-6658

DOCUMENT TYPE: Journal; Article

COUNTRY: United Kingdom

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT:
Fabry disease is a lysosomal storage disease arising from deficiency of the enzyme α- galactosidase A. Two recombinant protein therapeutics, Fabrazyme (agalsidase beta) and Replagal (agalsidase alfa), have been approved

in Europe as enzyme replacement therapies for Fabry disease. Both contain the same human enzyme, α-galactosidase A, but they are produced using different protein expression systems and have been approved for administration at different doses. To determine if there is recognizable biochemical basis for the different doses, we performed a comparison of the two drugs, focusing on factors that are likely to influence biological activity and availability. The two drugs have similar glycosylation, both in the type and location of the oligosaccharide structures present. Differences in glycosylation were mainly limited to the levels of sialic acid and mannose-6-phosphate present, with Fabrazyme having a higher percentage of fully sialylated oligosaccharides and a higher level of phosphorylation. The higher levels of phosphorylated oligomannose residues correlated with increased binding to mannose-6-phosphate receptors and uptake into Fabry fibroblasts in vitro. Biodistribution studies in a mouse model of Fabry disease showed similar organ uptake. Likewise, antigenicity studies using antisera from Fabry patients demonstrated that both drugs were indistinguishable in terms of antibody cross-reactivity. Based on these studies and present knowledge regarding the influence of glycosylation on protein biodistribution and cellular uptake, the two protein preparations appear to be functionally indistinguishable. Therefore, the data from these studies provide no rationale for the use of these proteins at different therapeutic doses.

CONTROLLED TERM: *Fabry disease; *alpha galactosidase; *agalsidase beta; *agalsidase alfa; biochemistry; enzyme replacement; lipid storage; protein expression; glycosylation; drug activity; drug bioavailability; enzyme phosphorylation; receptor binding; fibroblast; in vitro study; drug distribution; antigenicity; cross reaction; drug uptake; drug liver level; drug tissue level; human; nonhuman; mouse; animal experiment; animal model; controlled study; article; priority journal; glycolipid; oligosaccharide; sialic acid; mannose 6 phosphate; somatomedin B receptor; cross reacting antibody

CAS REGISTRY NUMBER: (alpha galactosidase) 9023-01-2; (agalsidase alfa) 104138-64-9; (mannose 6 phosphate) 3672-15-9

CHEMICAL NAME: Drug Trade Name: fabrazyme; replagal

CORPORATE NAME: Drug Manufacturer: Genzyme, United States; Transkaryotic Therapies, United States

L152 ANSWER 33 OF 37 BIOTECHNO COPYRIGHT 2010 Elsevier Science B.V. on STN DUPLICATE

ACCESSION NUMBER: 1994:24234410 BIOTECHNO Full-text

TITLE: Characterization of glycosylated and catalytically active recombinant human α-galactosidase A using a baculovirus vector

AUTHOR: Coppola G.; Yan Y.; Hantzopoulos P.; Segura E.; Stroh J.G.; Calhoun D.H.

CORPORATE SOURCE: Department of Chemistry, City College of New York, Convent Avenue and 138th Street,New York, NY 10031, United States.

SOURCE: Gene, (1994), 144/2 (197-203)
CODEN: GENED6 ISSN: 0378-1119

DOCUMENT TYPE: Journal; Article
COUNTRY: Netherlands
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
Fabry disease is an X-linked inborn error of glycolipid metabolism caused by a deficiency of the lysosomal enzyme α-galactosidase A (GalA: EC 3.2.1.22). In order to obtain large quantities of this human enzyme for physical characterization and for the development of new approaches for enzyme therapy, we constructed derivatives of the Autographa californica nuclear polyhedrosis virus that produce the human enzyme. The recombinant GalA (re-GalA) is produced at high levels, and is active with both the artificial substrate, 4-methylumbelliferyl-α-D- galactopyranoside, and the natural in vivo substrate, trihexosylceramide. The purified re-GalA is glycosylated and is taken up by normal and Fabry fibroblasts in cell culture. Mass spectral analysis of total monosaccharides released by hydrazinolysis indicates that it contains fucose, galactose, mannose and N- acetylglucosamine. Amino-acid sequence analysis of six proteolytic peptides corresponded to sequences predicted by the cDNA. The molecular masses of the purified enzyme, estimated by electrospray mass spectroscopy and laser desorption time-of-flight analysis are 46.85 and 46.62 kDa, respectively, approx. 10% greater than the polypeptide portion predicted by the cDNA. The recombinant enzyme retains significant catalytic activity after modification with poly(ethylene glycol), a treatment which decreases the immunogenicity and increases the circulation life of many proteins used therapeutically.
CONTROLLED TERM: *alpha galactosidase; *enzyme active site; *glycosylation; macrogol; article; autographa californica; baculovirus; enzyme analysis; enzyme purification; enzyme replacement; fabry disease; human; human cell; immunogenicity; inborn error of metabolism; lipid metabolism; mass spectrometry; polyhedrosis virus; priority journal; shuttle vector
CAS REGISTRY NUMBER: (alpha galactosidase) 9023-01-2; (macrogol) 25322-68-3

L152 ANSWER 34 OF 37 WPIX COPYRIGHT 2010 THOMSON REUTERS on STN
ACCESSION NUMBER: 2005-240849 [200525] WPIX
CROSS REFERENCE: 2003-090818; 2007-158346; 2009-E16922
TITLE: Treating lysosomal storage disease such as Fabry disease, Pompe disease, Krabbe disease, by administering lysosomal enzyme coupled to highly phosphorylated oligosaccharide derivatives containing mannose-6-phosphate, to subject
DERWENT CLASS: B04; D16
INVENTOR: ZHU Y
PATENT ASSIGNEE: (GENZ-C) GENZYME CORP
COUNTRY COUNT: 1

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 20050058634	A1	20050317	(200525)*	EN	33[17]	
US 7723296	B2	20100525	(201035)	EN		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 20050058634	A1 Provisional	US 2001-263078P	20010118
US 20050058634	A1 CIP of	US 2002-51711	20020117
US 20050058634	A1	US 2004-943893	20040920
US 7723296	B2 Provisional	US 2001-263078P	20010118
US 7723296	B2 CIP of	US 2002-51711	20020117
US 7723296	B2	US 2004-943893	20040920

FILING DETAILS:

PATENT NO	KIND		PATENT NO	
US 7723296	B2	CIP of	US 7001994	A

PRIORITY APPLN. INFO: US 2004-943893 20040920
US 2001-263078P 20010118
US 2002-51711 20020117

INT. PATENT CLASSIF.:
IPC ORIGINAL: A61K0031-17 [I,A]; A61K0031-17 [I,C]; A61K0031-429 [I,C]; A61K0031-43 [I,A]; C07K0001-00 [I,C]; C07K0001-107 [I,A]; C07K0001-113 [I,A]; C07K0014-435 [I,C]; C07K0014-47 [I,A]
IPC RECLASSIF.: C12P0021-00 [I,A]; C12P0021-00 [I,C]
ECLA: C12P0021-00B
USCLASS NCLM: 424/094.610; 514/007.000
NCLS: 514/008.000; 530/395.000; 530/411.000

BASIC ABSTRACT:

US 20050058634 A1 UPAB: 20090212
NOVELTY - Treating (M1) lysosomal storage disease in a subject comprising administering to the subject a lysosomal enzyme, where lysosomal enzyme is coupled to oligosaccharide by derivatizing an oligosaccharide comprising a phosphorylated hexose with compound containing carbonyl-reactive group, oxidizing lysosomal enzyme to generate carbonyl group on lysosomal enzyme, and reacting derivatized oligosaccharide with oxidized lysosomal enzyme, is new.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a modified acid alpha-glucosidase composition (I) comprising an acid alpha-glucosidase and a bis-mannose-6-phosphate (M6P) oligomannose, where the acid alpha-glucosidase and the bis-M6P oligomannose are linked by a hydrazone bond.
ACTIVITY - Nephrotropic; Cardiovascular-Gen.; CNS-Gen. Four to five month-old Pompe mice were used to evaluate the relative ability of recombinant human alpha-glucosidase (rhGAAs) to reduce glycogen storage in the affected tissue. Groups of Pompe mice (7 animals/groups) were injected through the tail vein with a vehicle and varying doses of rhGAA or modified rhGAA. Mice were administered three weekly doses and killed two weeks after the last treatment. Various tissues including the heart, diaphragm and skeletal muscles were collected and stored at -80 degrees Centigrade. The reduction in glycogen levels observed by biochemical analysis was confirmed by histomorphometric assessment of the quadriceps muscles obtained from the same animals. Tissue samples were stained for lysosomal glycogen followed by analysis of tissue by high resolution light microscopy (HRLM). This reduction was nearly as effective as the administration of 50 mg/kg of unmodified rhGAA which provided

for nearly a 60% reduction, suggesting that neo-rhGAA was 2 to 2.5 times more potent that rhGAA.
MECHANISM OF ACTION - None given.
USE - The lysosomal storage disease is chosen from Fabry disease, Pompe disease, Hurler or Hurler-Scheie disease, Krabbe disease, metachromatic leukodystrophy, Hunter disease, Sanfilippo A and B disease, Morquip A disease, Maroteaux-Lamy disease and Gaucher disease, preferably Pompe disease. The subject is a mammal (human) (claimed).
ADVANTAGE - In (M1), lysosomal enzymes are coupled to highly phosphorylated mannopyranosyl oligosaccharides containing M6P, to increase cellular uptake of lysosomal enzymes without destroying their biological activity.
TECHNOLOGY FOCUS:
BIOTECHNOLOGY - Preferred Method: In (M1), the lysosomal enzyme is acid alpha-glucosidase. The acid alpha-glucosidase is isolated from a natural source or produced recombinantly. The lysosomal enzyme comprises recombinant human acid alpha-glucosidase. The derivatized oligosaccharide comprises a synthetic oligosaccharide. The synthetic oligosaccharide comprises a bis-M6P oligomannose. The bis-M6P oligomannose is linked to the lysosomal enzyme by a hydrazone bond. The phosphorylated hexose is a terminal hexose or penultimate hexose. The phosphorylated hexose is M6P. The oligosaccharide comprises two or more M6P groups. The oxidizing step is carried out with periodate or galactose oxidase. The lysosomal enzyme is chosen from beta-glucocerebrosidase, alpha-galactosidase A, acid alpha-glucosidase, alpha-N-acetylglucosaminidase, beta-N-acetyl-hexosaminidase, and beta-glucuronidase. The oligosaccharide is chosen from a biantennary mannopyranosyl oligosaccharide and a trinatennary mannopyranosyl oligosaccharide. The biantennary mannopyranosyl oligosaccharide comprises bis-M6P. The triantennary mannopyrannosyl oligosaccharide comprises bis-M6P or tri-M6P. The oligosaccharide comprises 6-P-M (alpha 1,2)-M(alpha 1,3)-M, 6-P-M(alpha 1,2)-M(alpha 1,6)-, where M is mannose or a mannopyranosyl group. The derivatized oligosaccharide has a formula chosen from 6-P-Mn-R- and (6-P-Mx)mLn-R,
M = mannose or a mannopyranosyl group;
P = phosphate group linked to the 6C position of M;
L = hexose, preferably mannose, galactose, N-acetylglucosamine, and fucose;
R = compound containing at least one carbonyl-reactive group, m is 2-3;
n = 1-15, where if n greater than 1, Mn are linked to one another by alpha(1,2), alpha(1,3), alpha(1,4), or alpha(1,6);and
x = 1-15.
The compound containing at least one carbonyl-reactive group is chosen from a hydrazine, hydrazide, aminoxyl, semicarbozide. (M1) further involves adding a reducing agent to the coupled lysosomal enzyme. The reducing agent is cyanoborohydride.
FILE SEGMENT: CPI
MANUAL CODE: CPI: B04-C02X; B04-L05B; B14-N16; B14-S01; B14-S13; D05-A01A1; D05-A01B3

L152 ANSWER 35 OF 37 WPIX COPYRIGHT 2010 THOMSON REUTERS on STN
ACCESSION NUMBER: 2003-210100 [200320] WPIX
DOC. NO. CPI: C2003-053485 [200320]
TITLE: 7888uction of glycoproteins by culturing cells transformed with lysosomal enzyme yeast sugar-chain synthase variant, applicable as labeling marker for transporting lysozyme of cells and in drug compositions
DERWENT CLASS: B04; D16
INVENTOR: CHIBA Y; CHIKAMI Y; JIGAMI Y; KOBAYASHI K; SAKURABA H; TAKEUCHI M; TAKEUCHI Y; TAKEUCHI L R

PATENT ASSIGNEE: (KIRI-C) KIRIN BREWERY KK; (NIIT-C) NAT INST ADVANCED IND SCI & TECHNOLOGY; (NIIT-C) NAT INST ADVANCED IND SCI TECH; (NIIT-C) NAT INST ADVANCED IND SCI&TECHNOLOGY; (CHIB-I) CHIBA Y; (JIGA-I) JIGAMI Y; (KOBA-I) KOBAYASHI K; (SAKU-I) SAKURABA H; (TAKE-I) TAKEUCHI M; (TAKE-I) TAKEUCHI Y; (TOKM-N) TOKYO METROPOLITAN ORG MEDICAL RES; (TOKR-N) ZH TOKYOTO RINSHO IGAKU SOGO KENKYUSHO; (NIIT-C) DOKURITSU GYOSEI HOJIN SANGYO GIJUTSU SO

COUNTRY COUNT: 99

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2002103027	A1	20021227	(200320)*	JA	61[11]	
JP 2002369692	A	20021224	(200320)	JA	31	
EP 1408117	A1	20040414	(200426)	EN		
KR 2004026663	A	20040331	(200446)	KO		
AU 2002311219	A1	20030102	(200452)	EN		
CN 1541275	A	20041027	(200512)	ZH		
US 20050064539	A1	20050324	(200526)	EN		
CN 1298862	C	20070207	(200749)	ZH		
KR 888316	B1	20090311	(200924)	KO		
US 7579166	B2	20090825	(200956)	EN		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002103027	A1	WO 2002-JP5965	20020614
JP 2002369692	A	JP 2001-180907	20010614
AU 2002311219	A1	AU 2002-311219	20020614
CN 1541275	A	CN 2002-815803	20020614
CN 1298862	C	CN 2002-815803	20020614
EP 1408117	A1	EP 2002-736110	20020614
EP 1408117	A1	WO 2002-JP5965	20020614
US 20050064539	A1	WO 2002-JP5965	20020614
KR 888316	B1 PCT Application	WO 2002-JP5965	20020614
KR 2004026663	A	KR 2003-716258	20031212
KR 888316	B1	KR 2003-716258	20031212
US 20050064539	A1	US 2004-480790	20040624
US 7579166	B2 PCT Application	WO 2002-JP5965	20020614
US 7579166	B2	US 2004-480790	20040624

FILING DETAILS:

PATENT NO	KIND		PATENT NO
KR 888316	B1	Previous Publ	KR 2004026663 A
EP 1408117	A1	Based on	WO 2002103027 A
AU 2002311219	A1	Based on	WO 2002103027 A
KR 888316	B1	Based on	WO 2002103027 A
US 7579166	B2	Based on	WO 2002103027 A

PRIORITY APPLN. INFO: JP 2001-180907 20010614

INT. PATENT CLASSIF.:

MAIN: C12P021-00

SECONDARY: A61K038-00; A61K038-43; A61P043-00; C12P019-26

IPC ORIGINAL: A61K0038-00 [I,A]; A61K0038-00 [I,C]; A61K0038-43 [I,A]; A61K0038-43 [I,C]; A61P0043-00 [I,A]; A61P0043-00 [I,C];

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                           C07K0014-00 [N,A]; C07K0014-00 [N,C]; C12N0015-00 [I,A];
                           C12N0015-00 [I,C]; C12P0019-00 [I,C]; C12P0019-26 [I,A];
                           C12P0021-00 [I,A]; C12P0021-00 [I,C]; C12P0021-00 [I,A];
                           C12P0021-00 [I,C]; C12P0021-00 [I,A]; C12P0021-00 [I,C];
                           C12Q0001-68 [I,A]; C12Q0001-68 [I,C]
 IPC RECLASSIF.:           A61K0036-06 [I,C]; A61K0036-064 [I,A]; A61K0038-00 [I,A];
                           A61K0038-00 [I,C]; A61K0038-17 [I,A]; A61K0038-17 [I,C];
                           A61P0013-00 [I,C]; A61P0013-12 [I,A]; A61P0017-00 [I,A];
                           A61P0017-00 [I,C]; A61P0019-00 [I,A]; A61P0019-00 [I,C];
                           A61P0027-00 [I,C]; A61P0027-02 [I,A]; A61P0043-00 [I,A];
                           A61P0043-00 [I,C]; A61P0009-00 [I,A]; A61P0009-00 [I,C];
                           A61P0009-14 [I,A]; C08B0037-00 [I,A]; C08B0037-00 [I,C];
                           C12N0015-09 [I,A]; C12N0015-09 [I,C]; C12N0009-10 [I,A];
                           C12N0009-10 [I,C]; C12N0009-40 [I,A]; C12N0009-40 [I,C];
                           C12P0021-00 [I,A]; C12P0021-00 [I,C]
ECLA:                      A61K0035-78; A61K0036-064+M; A61K0038-17; C12N0009-10D1;
                           C12P0021-00B
ICO:                       K61K0038:00; M07K0207:00
USCLASS NCLM:              435/068.100; 435/069.100
        NCLS:              435/006.000; 435/069.100; 435/071.100; 435/254.200
JAP. PATENT CLASSIF.:
      MAIN/SEC.:           C12N0015-00 A (ZNA); A61K0037-02; A61P0013-12;
                           A61P0017-00; A61P0019-00; A61P0027-02; A61P0043-00 111;
                           A61P0009-00; A61P0009-14; C08B0037-00 P; C12N0009-40
FTERM CLASSIF.:            4B024; 4B050; 4C084; 4C090; 4C201; 4C206; 4B024/AA01;
                           4C084/AA01; 4C090/AA01; 4C084/AA02; 4C090/AA03;
                           4C084/AA06; 4C090/AA09; 4C084/BA01; 4C084/BA03;
                           4B024/BA12; 4C084/BA44; 4C084/BA48; 4C090/BA79;
                           4C090/BB14; 4C090/BB18; 4C090/BB32; 4C090/BB33;
                           4C090/BB34; 4C090/BB35; 4C090/BB36; 4C090/BB38;
                           4C090/BB64; 4C090/BB96; 4C090/BC17; 4C090/BD41;
                           4B024/CA04; 4C084/CA05; 4C084/CA18; 4C090/CA42;
                           4B050/CC03; 4C090/DA09; 4B024/DA12; 4C090/DA23;
                           4C084/DC50; 4B050/DD11; 4B024/EA04; 4B024/GA11;
                           4B024/HA01; 4B050/LL05; 4C084/NA14; 4C084/ZA33.1;
                           4C084/ZA36.1; 4C084/ZA81.1; 4C084/ZA89.1; 4C084/ZA96.1
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BASIC ABSTRACT:

WO 2002103027 A1   UPAB: 20090423

NOVELTY - Producing an active glycoprotein with an acidic sugar-chain containing a mannose-6-phosphate at its non-reducing terminal comprises using a yeast.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1) The glycoproteins produced by the new method, having an acidic sugar-chain containing mannose-6-phosphate at its non-reducing terminal; (2) Drug compositions for treating and/or preventing lysosomal diseases containing the glycoproteins; and (3) Producing active glycoproteins of formula (I)-(VII) having a high-mannose-type sugar-chain that contains a mannose-6-phosphate at its non-reducing terminal by using yeast. where

P = P(O)(OH)O2-.

ACTIVITY - Nephrotropic; Hemostatic. No biological data given.

MECHANISM OF ACTION - None given in source material.

USE - The produced glycoprotein is applicable as labeling marker for transporting lysozyme of mammalian cells and in drug compositions to treat human lysosomal enzyme deficiency e.g. Fabrys disease (claimed) and Gauchers disease.

ADVANTAGE - The lysosomal enzyme can be produced in large quantities for use as efficacious drugs. DESCRIPTION OF DRAWINGS - Common biosynthetic route of N-bonding sugar chain in mammals (as described by Konfeld et al.). (Drawing includes non-English language text). TECHNOLOGY FOCUS:

BIOTECHNOLOGY - Preferred Process: The

mannose-6-phosphate-containing acidic sugar-chain is particularly a sugar-chain obtained by binding to a mannose-6-phosphate receptor. The yeast is a strain that contains an acidic sugar-chain in at least the alpha-1,6-mannosyltransferase gene, and optionally a disrupted alpha-1,3-mannosyltransferase gene. Such alpha-1,6-mannosyltransferase is the OCH1 gene in S. cerevisiae, while the alpha1,3-mannosyltransferase gene is the MNN1 gene in S. cerevisiae. The yeast is particularly a mutant strain containing a highly-phosphorylated sugar-chain, e.g. S. cerevisiae HPY21 strain. The active glycoprotein with a mannose-6-phosphate-containing acidic sugar-chain is a lysosomal enzyme e.g. alpha-galactosidase. The structural gene of such alpha-galactosidase is a human-originated gene, such as one containing a base sequence of (V) with 1306 base pairs. The alpha-galactosidase is especially produced by a yeast of HPY21G strain. Such yeast-produced glycoprotein is treated with alpha-mannosidase to remove the mannose residue binding to the mannose-6-phosphate in the sugar-chain. The alpha-mannosidase particularly has an activity of removing a mannose residue binding to the mannose-1-phosphate or an activity of non-specific decomposition of alpha-1,2-mannoside linkage, alpha1,3-manoside linkage, or alpha1,6-mannoside linkage, which has exo-type activity but not endo-type activity. The alpha-mannosidase is originated from a bacterium belonging to Cellulomonas genus, e.g. Cellulomonas SO-5.

PHARMACEUTICALS - Preferred Drugs: The drug compositions contain the glycoprotein which is particularly a human alpha-galactosidase for treating Fabres disease.

EXTENSION ABSTRACT:

ADMINISTRATION - None given. EXAMPLE - A doubly mutated Saccharomyces cerevisiae for highly- phosphorylated sugar-chain biosynthesis in a S. cerevisiae DELTAochi DELTAmnn1 was constructed for transfer of an alpha-galactosidase gene. The transformant was then cultured to give a recombinant alpha-galactosidase for treatment with an alpha-mannosidase, and activity of the resulting protein was confirmed.

FILE SEGMENT: CPI
MANUAL CODE: CPI: B04-F0900E; B04-L03; B04-L04; B04-N0600E; B14-J01; B14-N10; B14-N12; B14-N15; D05-C12; D05-H17A6; D05-H17B6

L152 ANSWER 36 OF 37 WPIX COPYRIGHT 2010 THOMSON REUTERS on STN
ACCESSION NUMBER: 1994-340330 [199442] WPIX
CROSS REFERENCE: 1992-183672; 1994-200257
DOC. NO. CPI: C1994-155127 [199442]
TITLE: Recombinant human alpha-galactosidase A production - using a mammalian host cell expression system to obtain high yields of enzymatically active enzyme
DERWENT CLASS: B04; D16
INVENTOR: BISHOP D F; DESNICK R J; IOANNOU Y A
PATENT ASSIGNEE: (MOUN-C) MOUNT SINAI SCHOOL MEDICINE
COUNTRY COUNT: 1

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 5356804	A	19941018	(199442)*	EN	60[23]	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 5356804 A		US 1990-602824	19901024

PRIORITY APPLN. INFO: US 1990-602824 19901024
INT. PATENT CLASSIF.:
IPC RECLASSIF.: A61K0035-18 [I,A]; A61K0035-18 [I,C]; A61K0038-00 [N,A]; A61K0038-00 [N,C]; C12N0015-56 [I,A]; C12N0015-56 [I,C]; C12N0009-40 [I,A]; C12N0009-40 [I,C]
ECLA: A61K0035-18; C12N0009-40
ICO: K61K0038:00; M12N0207:00
BASIC ABSTRACT:

US 5356804 A UPAB: 20060109 (A) A mammalian cell is claimed comprising a chromosomally integrated nucleotide sequence encoding human alpha-galactosidase A (hAGA) controlled by a regulatory sequence that promotes gene expression and a selectable marker controlled by the same or different regulatory sequence, so that the hAGA nucleotide sequence is stably overexpressed and an enzymatically active hAGA enzyme is secreted by the mammalian cell.
(B) Also claimed is a method for producing hAGA, comprising (a) culturing a mammalian cell as in (A) and (b) isolating enzymatically active hAGA enzyme from the cell culture.
USE - The hAGA can be used for enzyme replacement therapy in patients with the lysosomal storage disorder, Fabry Disease. It can also be used in vitro to modify alpha-D-galacto-glyconjugates in a variety of processes, e.g. to convert blood gp. B erythrocytes to blood gp. O, or in commercial processes requiring the conversion of sugars such as raffinose to sucrose or melibiose to galactose and glucose.
ADVANTAGE - The mammalian host cell expression system provides for the appropriate co-translational and post-translational modifications required for proper processing, e.g. glycosylation, phosphorylation, etc. and sorting of the expression prod. so that an active enzyme is produced. Over 80% of the enzyme produced by the cells is secreted, providing high yields.

DOCUMENTATION ABSTRACT:

US5356804

(A) A mammalian cell is claimed comprising a chromosomally integrated nucleotide sequence encoding human alpha-galactosidase A (hAGA) controlled by a regulatory sequence that promotes gene expression and a selectable marker controlled by the same or different regulatory sequence, so that the hAGA nucleotide sequence is stably overexpressed and an enzymatically active hAGA enzyme is secreted by the mammalian cell.

Also claimed is a method for producing hAGA, comprising (a) culturing a mammalian cell as in (A) and (b) isolating enzymatically active hAGA enzyme from the cell culture.

USE

The hAGA can be used for enzyme replacement therapy in patients with the lysosomal storage disorder, Fabry Disease. It can also be used in vitro to modify alpha-D-galacto-glyconjugates in a variety of processes, e.g. to convert blood gp. B erythrocytes to blood gp. O, or in commercial processes requiring the conversion of sugars such as raffinose to sucrose or melibiose to galactose and glucose.

For therapy, hAGA can be used at a dose of e.g. 0.1 μg-10 mg, pref. 0.1-2 mg/kg.

ADVANTAGE

The mammalian host cell expression system provides for the appropriate co-translational and post-translational modifications required for proper processing, e.g. glycosylation, phosphorylation, etc. and sorting of the expression prod. so that an active enzyme is produced. Over 80% of the enzyme produced by the cells is secreted, providing high yields. The prefd. selectable marker is

dihydrofolate reductase (DHFR) and the selection is pref. with methotrexate.

EXAMPLE

A full length cDNA encoding hAGA was isolated from plasmid pcDAG126. A full length cDNA encoding hAGA from pcDAG126 was inserted into the expression vector p91023 (B) in front of the amplifiable DHFR cDNA. The p91-AGA construct obtd. was introduced by electroporation into DG44 dhfr-CHO cells. A clone was obtd. which expressed hAGA at a level of 1800 U/mg protein. (GS)

FILE SEGMENT: CPI

MANUAL CODE: CPI: B04-L05B0E; B14-L06; D05-H12A; D05-H12D5; D05-H14B2; D05-H17A3

L152 ANSWER 37 OF 37 DISSABS

ACCESSION NUMBER: 90:27561 DISSABS Order Number: AAR9108121

TITLE: EXPRESSION AND CHARACTERIZATION OF RECOMBINANT HUMAN ALPHA-GALACTOSIDASE A (GALACTOSIDE A)

AUTHOR: IOANNOU, YIANNIS ANDREAS [PH.D.]; BISHOP, DAVID F. [advisor]; DESNICK, ROBERT J. [advisor]

CORPORATE SOURCE: CITY UNIVERSITY OF NEW YORK (0046)

SOURCE: Dissertation Abstracts International, (1990) Vol. 51, No. 11B, p. 5136. Order No.: AAR9108121. 145 pages.

DOCUMENT TYPE: Dissertation

FILE SEGMENT: DAI

LANGUAGE: English

ENTRY DATE: Entered STN: 19921118
Last Updated on STN: 19921118

ABSTRACT:

Fabry disease, an X-linked inborn error of glycosphingolipid catabolism, results from the deficient activity of the lysosomal hydrolase, α-galactosidase A (α-Gal A). In order to characterize the normal enzyme and to evaluate the clinical effectiveness of enzyme replacement therapy, efforts were directed to produce large quantities of human recombinant α-Gal A. A full-length α-Gal A cDNA was inserted into the mammalian expression vector p91023(B) in front of the amplifiable dihydrofolate reductase (DHFR) cDNA. This construct was introduced into DG44 $dhfr\sp{-}$ CHO cells. Selected subclones were grown in increasing concentrations of methotrexate (MTX, 0.02 to 1.3 μM) resulting in co-amplification of DHFR and α-Gal A cDNAs. At a MTX concentration of 1.3 μM, 10$\sp7$ cells secreted $\sim$15,000 U/ml culture media/day. Using a hollow fiber bioreactor, up to 10 mg of enzyme protein was secreted per day.

The secreted α-Gal A was purified by affinity chromatography for characterization of various physical and kinetic properties. The recombinant enzyme had a pI of 3.9, a pH optimum of 4.6, a km of 1.9 mM toward 4-methylumbelliferyl-α-D-galactopyranoside and rapidly hydrolyzed globotriaosylceramide, the natural glycosphingolipid substrate. Pulse-chase studies indicated that the recombinant enzyme assumed its secondary structure in $< 3 min, was in the Golgi by 5

min where it became Endo H resistant, and was secreted into the media by 45-60 min. Labeling studies revealed that both the intracellular and secreted forms were phosphorylated. Further analysis revealed the presence of three N-linked oligosaccharide chains, two high-mannose type (Endo H sensitive) and one complex type. Analyses of the Endo H released oligosaccharides revealed that one had two phosphate residues and it specifically bound to immobililzed mannose-6-phosphate receptors while the other was a hybrid structure containing sialic acid. The secreted form of α-Gal A was taken up by cultured Fabry fibroblasts by a saturable process that was blocked in the presence of 2 mM mannose-6-phosphate. The availability of large amounts of soluble, active recombinant α-Gal A which is similar in structure to the native enzyme isolated from plasma will permit further comparison to the native enzyme forms and the clinical evaluation of enzyme replacement in Fabry disease.

CLASSIFICATION: 0369 BIOLOGY, GENETICS; 0307 BIOLOGY, MOLECULAR

TEXT SEARCH PART 2

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=> fil agricola pascal caba biotechno wpix biosis dissabs esbio embase scisearch
FILE 'AGRICOLA' ENTERED AT 11:07:13 ON 18 JUN 2010

FILE 'PASCAL' ENTERED AT 11:07:13 ON 18 JUN 2010
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=> d que l129; d que l146

L93        13980 SEA GALACTOSIDASE(A) A
L94          181 SEA RHGAA OR RH GAA
L100        7817 SEA RECEPTOR#(2A)(MANNOSE 6 PHOSPHATE OR (INSULIN LIKE GROWTH
                 FACTOR OR IGF)(A)(TYPE(W)(2 OR II)))
L102       41248 SEA (ACETYL(W) GLUCOSAMINE OR ACETYLGLUCOSAMINE)/BI
L103      132565 SEA GALACTOSE
L105          33 SEA (GLUCOSE OXIDASE)(A) A
L129           0 SEA L100 AND L102 AND L103 AND (L93 OR L94 OR L105)



L93        13980 SEA GALACTOSIDASE(A) A
L94          181 SEA RHGAA OR RH GAA
L96      1588404 SEA RECOMB?
L100        7817 SEA RECEPTOR#(2A)(MANNOSE 6 PHOSPHATE OR (INSULIN LIKE GROWTH
                 FACTOR OR IGF)(A)(TYPE(W)(2 OR II)))
L101       64594 SEA SIALIC ACID#
L102       41248 SEA (ACETYL(W) GLUCOSAMINE OR ACETYLGLUCOSAMINE)/BI
L103      132565 SEA GALACTOSE
L104      933367 SEA PHOSPHORYLAT?
L105          33 SEA (GLUCOSE OXIDASE)(A) A
L137          14 SEA L104 AND ((L93(5A) L96) OR L94 OR L105)
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L138          66 SEA L103 AND ((L93(5A) L96) OR L94 OR L105)
L139          44 SEA L100 AND ((L93(5A) L96) OR L94 OR L105)
L140          11 SEA ((L93(5A) L96) OR L94 OR L105) AND L101
L141           7 SEA ((L93(5A) L96) OR L94 OR L105) AND L102
L142          14 SEA L137 AND (L138 OR L139 OR L140 OR L141)
L143           7 SEA L138 AND (L139 OR L140 OR L141)
L144           3 SEA L139 AND (L140 OR L141)
L145           1 SEA L140 AND L141
L146          19 SEA (L142 OR L143 OR L144 OR L145)


=> s l146 not l126,l130,l132,l135

L153           7 L146 NOT (L126 OR L130 OR L132 OR L135)      L126,L130,L132,L135
                                                              WERE PREVIOUSLY PRINTED

=> fil hcapl; d que l50; d que l52; s l50,l52 not l29,l23,l33

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FILE COVERS 1907 - 18 Jun 2010  VOL 152 ISS 26
FILE LAST UPDATED: 17 Jun 2010  (20100617/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Apr 2010
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Apr 2010

HCAplus now includes complete International Patent Classification (IPC)
reclassification data for the second quarter of 2010.

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'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE


L7           189 SEA FILE=REGISTRY SPE=ON  ABB=ON  GALACTOSIDASE, A?/CN
L9          4266 SEA FILE=HCAPLUS SPE=ON  ABB=ON  L7
L10         3364 SEA FILE=HCAPLUS SPE=ON  ABB=ON  GALACTOSIDASE/OBI(L)A/OB
                 I
L11            9 SEA FILE=HCAPLUS SPE=ON  ABB=ON  RHGAA/OBI OR RH GAA/OBI
L12            7 SEA FILE=HCAPLUS SPE=ON  ABB=ON  GLUCOSE OXIDASE/OBI(L)A/
                 OBI(L)ACID?/OBI
L13       212052 SEA FILE=HCAPLUS SPE=ON  ABB=ON  RECOMB?/OBI
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L14     1993781 SEA FILE=HCAPLUS SPE=ON  ABB=ON  HUMAN/OBI
L18          31 SEA FILE=HCAPLUS SPE=ON  ABB=ON  GGA/OBI(L)(L13 OR L14)
L36           1 SEA FILE=REGISTRY SPE=ON  ABB=ON  ACETYLGLUCOSAMINE/CN
L37        7785 SEA FILE=HCAPLUS SPE=ON  ABB=ON  L36
L38       15302 SEA FILE=HCAPLUS SPE=ON  ABB=ON  (ACETYL(W)GLUCOSAMINE OR
                ACETYLGLUCOSAMINE)/BI
L39       23161 SEA FILE=HCAPLUS SPE=ON  ABB=ON  (SIALIC ACID#)/BI
L40           2 SEA FILE=REGISTRY SPE=ON  ABB=ON  GALACTOSE/CN
L41       29474 SEA FILE=HCAPLUS SPE=ON  ABB=ON  L40
L42       64930 SEA FILE=HCAPLUS SPE=ON  ABB=ON  GALACTOSE/BI
L43         132 SEA FILE=HCAPLUS SPE=ON  ABB=ON  (L9 OR L10 OR L11 OR L12 OR
                L18) AND (L37 OR L38)
L44          82 SEA FILE=HCAPLUS SPE=ON  ABB=ON  (L9 OR L10 OR L11 OR L12 OR
                L18) AND L39
L45         811 SEA FILE=HCAPLUS SPE=ON  ABB=ON  (L9 OR L10 OR L11 OR L12 OR
                L18) AND (L41 OR L42)
L46          22 SEA FILE=HCAPLUS SPE=ON  ABB=ON  L43 AND L44 AND L45
L49      243556 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PHOSPHORYLAT?/BI
L50           3 SEA FILE=HCAPLUS SPE=ON  ABB=ON  L46 AND L49



L7          189 SEA FILE=REGISTRY SPE=ON  ABB=ON  GALACTOSIDASE, A?/CN
L9         4266 SEA FILE=HCAPLUS SPE=ON  ABB=ON  L7
L10        3364 SEA FILE=HCAPLUS SPE=ON  ABB=ON  GALACTOSIDASE/OBI(L)A/OB
                I
L11           9 SEA FILE=HCAPLUS SPE=ON  ABB=ON  RHGAA/OBI OR RH GAA/OBI
L12           7 SEA FILE=HCAPLUS SPE=ON  ABB=ON  GLUCOSE OXIDASE/OBI(L)A/
                OBI(L)ACID?/OBI
L13      212052 SEA FILE=HCAPLUS SPE=ON  ABB=ON  RECOMB?/OBI
L14     1993781 SEA FILE=HCAPLUS SPE=ON  ABB=ON  HUMAN/OBI
L18          31 SEA FILE=HCAPLUS SPE=ON  ABB=ON  GGA/OBI(L)(L13 OR L14)
L34        1039 SEA FILE=HCAPLUS SPE=ON  ABB=ON  RECEPTOR#/OBI(L)(MANNOSE 6
                PHOSPHATE/OBI)
L49      243556 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PHOSPHORYLAT?/BI
L51          20 SEA FILE=HCAPLUS SPE=ON  ABB=ON  L34 AND (L9 OR L10 OR L11 OR
                L12 OR L18)
L52           6 SEA FILE=HCAPLUS SPE=ON  ABB=ON  L51 AND (L49 OR L13)



L154          8 (L50 OR L52) NOT (L29 OR L23 OR L33)       L29,L23,L33 WERE
                                                           PREVIOUSLY PRINTED

=> fil medl; d que 179; d que 189

FILE 'MEDLINE' ENTERED AT 11:07:18 ON 18 JUN 2010

 FILE LAST UPDATED: 17 Jun 2010 (20100617/UP).  FILE COVERS 1947 TO DATE.

 MEDLINE and LMEDLINE have been updated with the 2010 Medical Subject
 Headings (MeSH) vocabulary and tree numbers from the U.S.  National Library
 of Medicine (NLM).  Additional information is available at

 http://www.nlm.nih.gov/pubs/techbull/nd09/nd09_medline_data_changes_2010.html.

 The Medline file has been reloaded effective January 24, 2010.  See HELP
 RLOAD for details.
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This file contains CAS Registry Numbers for easy and accurate
substance identification.

See HELP RANGE before carrying out any RANGE search.

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L59        3349 SEA FILE=MEDLINE SPE=ON  ABB=ON  ALPHA-GLUCOSIDASES/CT
L60          35 SEA FILE=MEDLINE SPE=ON  ABB=ON  RHGAA OR RH GAA
L67        9132 SEA FILE=MEDLINE SPE=ON  ABB=ON  PROTEIN ENGINEERING/CT
L68      141392 SEA FILE=MEDLINE SPE=ON  ABB=ON  RECOMBINANT PROTEINS/CT
L75        1573 SEA FILE=MEDLINE SPE=ON  ABB=ON  RECEPTOR, IGF TYPE 2/CT
L79           6 SEA FILE=MEDLINE SPE=ON  ABB=ON  L59 AND (L60 OR L67 OR L68)
                AND L75
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L59        3349 SEA FILE=MEDLINE SPE=ON  ABB=ON  ALPHA-GLUCOSIDASES/CT
L60          35 SEA FILE=MEDLINE SPE=ON  ABB=ON  RHGAA OR RH GAA
L67        9132 SEA FILE=MEDLINE SPE=ON  ABB=ON  PROTEIN ENGINEERING/CT
L68      141392 SEA FILE=MEDLINE SPE=ON  ABB=ON  RECOMBINANT PROTEINS/CT
L83       17338 SEA FILE=MEDLINE SPE=ON  ABB=ON  SIALIC ACID#
L84       28806 SEA FILE=MEDLINE SPE=ON  ABB=ON  GALACTOSE#
L85       10499 SEA FILE=MEDLINE SPE=ON  ABB=ON  ACETYL GLUCOSAMINE OR
                ACETYLGLUCOSAMINE
L89           5 SEA FILE=MEDLINE SPE=ON  ABB=ON  L59 AND (L60 OR L67 OR L68)
                AND (L83 OR L84 OR L85)
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=> s l79,l89 not l70,l74,l64

L155          8 (L79 OR L89) NOT (L70 OR L74 OR L64)        l70,L74,L64 WERE
                                                             PREVIOUSLY PRINTED


=> => dup rem l155,l154,l153
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PROCESSING COMPLETED FOR L155
PROCESSING COMPLETED FOR L154
PROCESSING COMPLETED FOR L153
L156         18 DUP REM L155 L154 L153 (5 DUPLICATES REMOVED)
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ANSWERS '1-8' FROM FILE MEDLINE
ANSWERS '9-16' FROM FILE HCAPLUS
ANSWER '17' FROM FILE BIOTECHNO
ANSWER '18' FROM FILE ESBIOBASE

=> d iall 1-8; d ibib ab hitind 9-16; d iall 17-18; fil hom

L156 ANSWER 1 OF 18 MEDLINE on STN
ACCESSION NUMBER: 2007469808 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 17658854
TITLE: New synthetic routes to chain-extended selenium, sulfur, and nitrogen analogues of the naturally occurring glucosidase inhibitor salacinol and their inhibitory activities against recombinant human maltase glucoamylase.
AUTHOR: Liu Hui; Nasi Ravindranath; Jayakanthan Kumarasamy; Sim Lyann; Heipel Heather; Rose David R; Pinto B Mario
CORPORATE SOURCE: Department of Chemistry, Simon Fraser University, Burnaby, British Columbia, Canada V5A 1S6.
SOURCE: The Journal of organic chemistry, (2007 Aug 17) Vol. 72, No. 17, pp. 6562-72. Electronic Publication: 2007-07-21. Journal code: 2985193R. ISSN: 0022-3263. L-ISSN: 0022-3263.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200710
ENTRY DATE: Entered STN: 11 Aug 2007
Last Updated on STN: 26 Oct 2007
Entered Medline: 25 Oct 2007
ABSTRACT:
Six heteroanalogues (X = S, Se, NH) of the naturally occurring glucosidase inhibitor salacinol, containing polyhydroxylated, acyclic chains of 6-carbons, were synthesized for structure-activity studies with different glycosidase enzymes. The target zwitterionic compounds were synthesized by means of nucleophilic attack of the PMB-protected 1,4-anhydro-4-seleno-, 1,4-anhydro-4-thio-, and 1,4-anhydro-4-imino-D-arabinitols at the least hindered carbon atom of 1,3-cyclic sulfates. These 1,3-cyclic sulfates were derived from D-glucose and D-galactose, and significantly, they utilized butane diacetal as the protecting groups for the trans 2,3-diequatorial positions. Deprotection of the coupled products proceeded smoothly, unlike in previous attempts with different protecting groups, and afforded the target selenonium, sulfonium, and ammonium sulfates with different stereochemistry at the stereogenic centers. The four new heterosubstituted compounds (X = Se, NH) inhibited recombinant human maltase glucoamylase (MGA), one of the key intestinal enzymes involved in the breakdown of glucose oligosaccharides in the small intestine. The two selenium derivatives each had Ki values of 0.10 microM, giving the most active compounds to date in this general series of zwitterionic glycosidase inhibitors. The two nitrogen compounds also inhibited MGA but were less active, with Ki values of 0.8 and 35 microM. The compounds in which X = S showed Ki values of 0.25 and 0.17 microM. Comparison of these data with those reported previously for related compounds reinforces the requirements for an effective inhibitor of MGA. With respect to chain extension, the configurations at C-2' and C-4' are critical for activity, the configuration at C-3', bearing the sulfate moiety, being unimportant. It would also appear that the configuration at C-5' is important but the relationship is dependent on the heteroatom.
CONTROLLED TERM: *Enzyme Inhibitors: CS, chemical synthesis
Enzyme Inhibitors: CH, chemistry
Enzyme Inhibitors: PD, pharmacology

Humans
Magnetic Resonance Spectroscopy
*Nitrogen: CH, chemistry
Recombinant Proteins: AI, antagonists & inhibitors
*Selenium: CH, chemistry
Spectrometry, Mass, Matrix-Assisted Laser Desorption-Ionization
*Sugar Alcohols: CS, chemical synthesis
Sugar Alcohols: CH, chemistry
Sugar Alcohols: PD, pharmacology
*Sulfates: CS, chemical synthesis
Sulfates: CH, chemistry
Sulfates: PD, pharmacology
*Sulfur: CH, chemistry
*alpha-Glucosidases: AI, antagonists & inhibitors

CAS REGISTRY NO.: 7704-34-9 (Sulfur); 7727-37-9 (Nitrogen); 7782-49-2 (Selenium)
CHEMICAL NAME: 0 (Enzyme Inhibitors); 0 (Recombinant Proteins); 0 (Sugar Alcohols); 0 (Sulfates); 0 (salacinol); EC 3.2.1.20 (alpha-Glucosidases)

L156 ANSWER 2 OF 18 MEDLINE on STN
ACCESSION NUMBER: 2007321510 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 17293352
TITLE: N-glycans of recombinant human acid alpha-glucosidase expressed in the milk of transgenic rabbits.
AUTHOR: Jongen Susanne P; Gerwig Gerrit J; Leeflang Bas R; Koles Kate; Mannesse Maurice L M; van Berkel Patrick H C; Pieper Frank R; Kroos Marian A; Reuser Arnold J J; Zhou Qun; Jin Xiaoying; Zhang Kate; Edmunds Tim; Kamerling Johannis P
CORPORATE SOURCE: Bijvoet Center for Biomolecular Research, Department of Bio-Organic Chemistry, Utrecht University, Padualaan 8, NL-3584 CH Utrecht, The Netherlands.
SOURCE: Glycobiology, (2007 Jun) Vol. 17, No. 6, pp. 600-19.
Electronic Publication: 2007-02-09.
Journal code: 9104124. ISSN: 0959-6658. L-ISSN: 0959-6658.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200708
ENTRY DATE: Entered STN: 31 May 2007
Last Updated on STN: 10 Aug 2007
Entered Medline: 9 Aug 2007

ABSTRACT:
Pompe disease is a lysosomal glycogen storage disorder characterized by acid alpha-glucosidase (GAA) deficiency. More than 110 different pathogenic mutations in the gene encoding GAA have been observed. Patients with this disease are being treated by intravenous injection of recombinant forms of the enzyme. Focusing on recombinant approaches to produce the enzyme means that specific attention has to be paid to the generated glycosylation patterns. Here, human GAA was expressed in the mammary gland of transgenic rabbits. The N-linked glycans of recombinant human GAA (rhAGLU), isolated from the rabbit milk, were released by peptide-N(4)-(N-acetyl-beta-glucosaminyl)asparagine amidase F. The N-glycan pool was fractionated and purified into individual components by a combination of anion-exchange, normal-phase, and Sambucus nigra agglutinin-affinity chromatography. The structures of the components were analyzed by 500 MHz one-dimensional and 600 MHz cryo two-dimensional (total correlation spectroscopy [TOCSY] nuclear Overhauser enhancement spectroscopy) (1)H nuclear magnetic resonance spectroscopy, combined with two-dimensional

(31)P-filtered (1)H-(1)H TOCSY spectroscopy, matrix-assisted laser desorption ionization time-of-flight mass spectrometry, and high-performance liquid chromatography (HPLC)-profiling of 2-aminobenzamide-labeled glycans combined with exoglycosidase digestions. The recombinant rabbit glycoprotein contained a broad array of different N-glycans, comprising oligomannose-, hybrid-, and complex-type structures. Part of the oligomannose-type glycans showed the presence of phospho-diester-bridged N-acetylglucosamine. For the complex-type glycans (partially) (alpha2-6)-sialylated (nearly only N-acetylneuraminic acid) diantennary structures were found; part of the structures were (alpha1-6)-core-fucosylated or (alpha1-3)-fucosylated in the upper antenna (Lewis x). Using HPLC-mass spectrometry of glycopeptides, information was generated with respect to the site-specific location of the various glycans.

CONTROLLED TERM: Check Tags: Female
Animals
Animals, Genetically Modified
Carbohydrate Conformation
Carbohydrate Sequence
Chromatography, Affinity
Chromatography, High Pressure Liquid
Chromatography, Ion Exchange
Glycosylation
Humans
Mammary Glands, Animal: ME, metabolism
Mass Spectrometry
*Milk: CH, chemistry
Nuclear Magnetic Resonance, Biomolecular
Peptide-N4-(N-acetyl-beta-glucosaminyl) Asparagine Amidase: PD, pharmacology
*Polysaccharides: CH, chemistry
Polysaccharides: IP, isolation & purification
*Polysaccharides: ME, metabolism
Rabbits
Recombinant Proteins: CH, chemistry
Recombinant Proteins: IP, isolation & purification
Recombinant Proteins: ME, metabolism
Spectrometry, Mass, Matrix-Assisted Laser Desorption-Ionization
*alpha-Glucosidases: CH, chemistry
alpha-Glucosidases: GE, genetics
*alpha-Glucosidases: ME, metabolism

CHEMICAL NAME: 0 (Polysaccharides); 0 (Recombinant Proteins); EC 3.2.1.20 (GAA protein, human); EC 3.2.1.20 (alpha-Glucosidases); EC 3.5.1.52 (Peptide-N4-(N-acetyl-beta-glucosaminyl) Asparagine Amidase)

L156 ANSWER 3 OF 18 MEDLINE on STN
ACCESSION NUMBER: 2006224193 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16507578
TITLE: Structural requirements for efficient processing and activation of recombinant human UDP-N-acetylglucosamine:lysosomal-enzyme-N-acetylglucosamine-1-phosphotransferase.
AUTHOR: Kudo Mariko; Canfield William M
CORPORATE SOURCE: Genzyme Corporation, Oklahoma City, Oklahoma 73104, USA.
SOURCE: The Journal of biological chemistry, (2006 Apr 28) Vol. 281, No. 17, pp. 11761-8. Electronic Publication: 2006-02-28.
Journal code: 2985121R. ISSN: 0021-9258. L-ISSN: 0021-9258.
PUB. COUNTRY: United States

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DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200607
ENTRY DATE:         Entered STN: 25 Apr 2006
                    Last Updated on STN: 6 Jul 2006
                    Entered Medline: 5 Jul 2006
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ABSTRACT:

Mannose 6-phosphate-modified N-glycans are the determinant for intracellular targeting of newly synthesized lysosomal hydrolases to the lysosome. The enzyme responsible for the initial step in the synthesis of mannose 6-phosphate is UDP-N-acetylglucosamine:lysosomal-enzyme-N-acetylglucosmine-1-phosphotransferase(GlcNAc-phosphotransferase). GlcNAc-phosphotransferase is a multisubunit enzyme with an alpha2beta2gamma2 arrangement that requires a detergent for solubilization. Recent cloning of cDNAs and genes encoding these subunits revealed that the alpha- and beta-subunits are encoded by a single gene as a precursor, whereas the gamma-subunit is encoded by a second gene. The hydropathy plots of the deduced amino acid sequences suggested that the alpha- and beta-subunits but not the gamma-subunit contain transmembrane domains. Access to these cDNAs allowed us to express a soluble form of human recombinant GlcNAc-phosphotransferase by removing the putative transmembrane and cytoplasmic domains from the alpha- and beta-subunits. Because this modification prevented precursor processing to mature alpha- and beta-subunits, the native cleavage sequence was replaced by a cleavage site for furin. When the modified alpha/beta-subunits (alpha'/beta'-subunits) precursor and wild type gamma-subunit cDNAs were co-expressed in 293T or CHO-K1 cells, a furin-like protease activity in these cells cleaved the precursor and produced an active and processed soluble GlcNAc-phosphotransferase with an alpha'2beta'2gamma2-subunits arrangement. Recombinant soluble GlcNAc-phosphotransferase exhibited specific activity and substrate preferences similar to the wild type bovine GlcNAc-phosphotransferase and was able to phosphorylate a lysosomal hydrolase, acid alpha-glucosidase in vitro.

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CONTROLLED TERM:     Amino Acid Sequence
                     Animals
                     CHO Cells: EN, enzymology
                     Cattle
                     Cricetinae
                     DNA, Complementary
                     Humans
                     Hydrolases: ME, metabolism
                     Lysosomes: EN, enzymology
                     Molecular Sequence Data
                     Phosphorylation
                    *Protein Processing, Post-Translational
                     Protein Subunits
                       Recombinant Proteins: GE, genetics
                       Recombinant Proteins: IP, isolation & purification
                       Recombinant Proteins: ME, metabolism
                     Sequence Homology, Amino Acid
                     Substrate Specificity
                    *Transferases (Other Substituted Phosphate Groups)
                     Transferases (Other Substituted Phosphate Groups): CH,
                    chemistry
                     Transferases (Other Substituted Phosphate Groups): GE,
                    genetics
                     Transferases (Other Substituted Phosphate Groups): ME,
                    metabolism
                       alpha-Glucosidases: ME, metabolism
CHEMICAL NAME:      0 (DNA, Complementary); 0 (Protein Subunits); 0
                    (Recombinant Proteins); EC 2.7.8.- (Transferases (Other
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Substituted Phosphate Groups)); EC 2.7.8.17 (UDP-N-acetylglucosamine-lysosomal-enzyme-N-acetylglucosaminephosphotransferase); EC 3.- (Hydrolases); EC 3.2.1.20 (alpha-Glucosidases)

L156 ANSWER 4 OF 18 MEDLINE on STN

ACCESSION NUMBER: 2005378812 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 15839836

TITLE: Carbohydrate-remodelled acid alpha-glucosidase with higher affinity for the cation-independent mannose 6-phosphate receptor demonstrates improved delivery to muscles of Pompe mice.

AUTHOR: Zhu Yunxiang; Li Xuemei; McVie-Wylie Alison; Jiang Canwen; Thurberg Beth L; Raben Nina; Mattaliano Robert J; Cheng Seng H

CORPORATE SOURCE: Genzyme Corporation, 31 New York Avenue, Framingham, MA 01701-9322, USA.

SOURCE: The Biochemical journal, (2005 Aug 1) Vol. 389, No. Pt 3, pp. 619-28.
Journal code: 2984726R. E-ISSN: 1470-8728. L-ISSN: 0264-6021.
Report No.: NLM-PMC1180711.

PUB. COUNTRY: England: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200511

ENTRY DATE: Entered STN: 23 Jul 2005
Last Updated on STN: 5 Nov 2005
Entered Medline: 4 Nov 2005

ABSTRACT:

To enhance the delivery of rhGAA (recombinant GAA, where GAA stands for acid alpha-glucosidase) to the affected muscles in Pompe disease, the carbohydrate moieties on the enzyme were remodelled to exhibit a high affinity ligand for the CI-MPR (cation-independent M6P receptor, where M6P stands for mannose 6-phosphate). This was achieved by chemically conjugating on to ***rhGAA*** , a synthetic oligosaccharide ligand bearing M6P residues in the optimal configuration for binding the receptor. The carbonyl chemistry used resulted in the conjugation of approx. six synthetic ligands on to each enzyme. The resulting modified enzyme [neo-rhGAA (modified recombinant human GAA harbouring synthetic oligosaccharide ligands)] displayed near-normal specific activity and significantly increased affinity for the CI-MPR. However, binding to the mannose receptor was unaffected despite the introduction of additional mannose residues in neo-rhGAA. Uptake studies using L6 myoblasts showed neo-rhGAA was internalized approx. 20-fold more efficiently than the unmodified enzyme. Administration of neo-***rhGAA*** into Pompe mice also resulted in greater clearance of glycogen from all the affected muscles when compared with the unmodified rhGAA . Comparable reductions in tissue glycogen levels in the Pompe mice were realized using an approx. 8-fold lower dose of neo-rhGAA in the heart and diaphragm and an approx. 4-fold lower dose in the skeletal muscles. Treatment of older Pompe mice, which are more refractory to enzyme therapy, with 40 mg/kg neo-rhGAA resulted in near-complete clearance of glycogen from all the affected muscles as opposed to only partial correction with the unmodified rhGAA. These results demonstrate that remodelling the carbohydrate of rhGAA to improve its affinity for the CI-MPR represents a feasible approach to enhance the efficacy of enzyme replacement therapy for Pompe disease.

CONTROLLED TERM: Aging

Animals
*Glucan 1,4-alpha-Glucosidase: CH, chemistry
*Glucan 1,4-alpha-Glucosidase: ME, metabolism
Glucan 1,4-alpha-Glucosidase: TU, therapeutic use
Glycogen: ME, metabolism
*Glycogen Storage Disease Type II: DT, drug therapy
Glycogen Storage Disease Type II: ME, metabolism
Mice
Molecular Structure
Muscle, Skeletal: EN, enzymology
*Muscle, Skeletal: ME, metabolism
Myocardium: EN, enzymology
Myocardium: ME, metabolism
Oligosaccharides
Protein Binding
Receptor, IGF Type 2: CH, chemistry
*Receptor, IGF Type 2: ME, metabolism
Recombinant Proteins
alpha-Glucosidases

CAS REGISTRY NO.: 9005-79-2 (Glycogen)
CHEMICAL NAME: 0 (Oligosaccharides); 0 (Receptor, IGF Type 2); 0 (Recombinant Proteins); EC 3.2.1.20 (alpha-Glucosidases); EC 3.2.1.3 (Glucan 1,4-alpha-Glucosidase)

L156 ANSWER 5 OF 18 MEDLINE on STN
ACCESSION NUMBER: 2003491775 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 14567965
TITLE: Enzyme replacement therapy in the mouse model of Pompe disease.
AUTHOR: Raben N; Danon M; Gilbert A L; Dwivedi S; Collins B; Thurberg B L; Mattaliano R J; Nagaraju K; Plotz P H
CORPORATE SOURCE: Arthritis and Rheumatism Branch, National Institutes of Health, US HHS NIH NIAMS, 9000 Rockville Pike, Bld 10/9N244, Bethesda, MD 20892, USA.. rabenn@arb.niams.nih.gov
SOURCE: Molecular genetics and metabolism, (2003 Sep-Oct) Vol. 80, No. 1-2, pp. 159-69.
Journal code: 9805456. ISSN: 1096-7192. L-ISSN: 1096-7192.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200411
ENTRY DATE: Entered STN: 22 Oct 2003
Last Updated on STN: 19 Dec 2003
Entered Medline: 16 Nov 2004

ABSTRACT:
Deficiency of acid alpha-glucosidase (GAA) results in widespread cellular deposition of lysosomal glycogen manifesting as myopathy and cardiomyopathy. When GAA-/- mice were treated with rhGAA (20 mg/kg/week for up to 5 months), skeletal muscle cells took up little enzyme compared to liver and heart. Glycogen reduction was less than 50%, and some fibers showed little or no glycogen clearance. A dose of 100 mg/kg/week resulted in approximately 75% glycogen clearance in skeletal muscle. The enzyme reduced cardiac glycogen to undetectable levels at either dose. Skeletal muscle fibers with residual glycogen showed immunoreactivity for LAMP-1/LAMP-2, indicating that undigested glycogen remained in proliferating lysosomes. Glycogen clearance was more pronounced in type 1 fibers, and histochemical analysis suggested an increased mannose-6-phosphate receptor immunoreactivity in these fibers. Differential transport of enzyme into lysosomes may explain the strikingly uneven pattern of

glycogen removal. Autophagic vacuoles, a feature of both the mouse model and the human disease, persisted despite glycogen clearance. In some groups a modest glycogen reduction was accompanied by improved muscle strength. These studies suggest that enzyme replacement therapy, although at much higher doses than in other lysosomal diseases, has the potential to reverse cardiac pathology and to reduce the glycogen level in skeletal muscle.

CONTROLLED TERM: Animals
Antigens, CD: BI, biosynthesis
Autophagy: PH, physiology
Disease Models, Animal
Glycogen: ME, metabolism
*Glycogen Storage Disease Type II: DT, drug therapy
Glycogen Storage Disease Type II: EN, enzymology
Glycogen Storage Disease Type II: GE, genetics
Humans
*Liver: EN, enzymology
Liver: PA, pathology
Lysosome-Associated Membrane Glycoproteins
Lysosomes: EN, enzymology
Mice
Muscle, Skeletal: DE, drug effects
*Muscle, Skeletal: EN, enzymology
Muscle, Skeletal: PA, pathology
*Myocardium: EN, enzymology
Myocardium: PA, pathology
Receptor, IGF Type 2: BI, biosynthesis
Recombinant Proteins: ME, metabolism
Recombinant Proteins: PD, pharmacology
*alpha-Glucosidases: DF, deficiency
alpha-Glucosidases: ME, metabolism
alpha-Glucosidases: PD, pharmacology

CAS REGISTRY NO.: 9005-79-2 (Glycogen)
CHEMICAL NAME: 0 (Antigens, CD); 0 (Lysosome-Associated Membrane Glycoproteins); 0 (Receptor, IGF Type 2); 0 (Recombinant Proteins); EC 3.2.1.20 (alpha-Glucosidases)

L156 ANSWER 6 OF 18 MEDLINE on STN
ACCESSION NUMBER: 2001055755 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 10972187
TITLE: Thermotoga maritima AglA, an extremely thermostable NAD+-, Mn2+-, and thiol-dependent alpha-glucosidase.
AUTHOR: Raasch C; Streit W; Schanzer J; Bibel M; Gosslar U; Liebl W
CORPORATE SOURCE: Institut fur Mikrobiologie und Genetik, Georg-August-Universitat, Gottingen, Germany.
SOURCE: Extremophiles : life under extreme conditions, (2000 Aug) Vol. 4, No. 4, pp. 189-200.
Journal code: 9706854. ISSN: 1431-0651. L-ISSN: 1431-0651.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
OTHER SOURCE: GENBANK-AJ001089
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 21 Dec 2000

ABSTRACT:
The gene for the alpha-glucosidase AglA of the hyperthermophilic bacterium Thermotoga maritima MSB8, which was identified by phenotypic screening of a T.

maritima gene library, is located within a cluster of genes involved in the hydrolysis of starch and maltodextrins and the uptake of maltooligosaccharides. According to its primary structure as deduced from the nucleotide sequence of the gene, AglA belongs to family 4 of glycosyl hydrolases. The enzyme was recombinantly expressed in Escherichia coli, purified, and characterized. The T. maritima alpha-glucosidase has the unusual property of requiring NAD+ and Mn2+ for activity. Co2+ and Ni2+ also activated AglA, albeit less efficiently than Mn2+. T. maritima AglA represents the first example of a maltodextrin-degrading alpha-glucosidase with NAD+ and Mn2+ requirement. In addition, AglA activity depended on reducing conditions. This third requirement was met by the addition of dithiothreitol (DTT) or beta-mercaptoethanol to the assay. Using gel permeation chromatography, T. maritima AglA behaved as a dimer (two identical 55-kDa subunits), irrespective of metal depletion or metal addition, and irrespective of the presence or absence of NAD+ or DTT. The enzyme hydrolyzes maltose and other small maltooligosaccharides but is inactive against the polymeric substrate starch. AglA is not specific with respect to the configuration at the C-4 position of its substrates because glycosidic derivatives of D-galactose are also hydrolyzed. In the presence of all cofactors, maximum activity was recorded at pH 7.5 and 90 degrees C (4-min assay). AglA is the most thermoactive and the most thermostable member of glycosyl hydrolase family 4. When incubated at 50 degrees C and 70 degrees C, the recombinant enzyme suffered partial inactivation during the first hours of incubation, but thereafter the residual activity did not drop below about 50% and 20% of the initial value, respectively, within a period of 48 h.

CONTROLLED TERM: Cations, Divalent: ME, metabolism
Cations, Divalent: PD, pharmacology
Dithiothreitol: PD, pharmacology
Enzyme Stability: DE, drug effects
Escherichia coli
Genes, Bacterial
Hydrogen-Ion Concentration
Kinetics
Manganese: ME, metabolism
*Manganese: PD, pharmacology
Molecular Sequence Data
Multigene Family
NAD: ME, metabolism
*NAD: PD, pharmacology
Recombinant Proteins: IP, isolation & purification
Recombinant Proteins: ME, metabolism
Sequence Analysis, DNA
Substrate Specificity
Sulfhydryl Compounds: ME, metabolism
*Sulfhydryl Compounds: PD, pharmacology
Temperature
*Thermotoga maritima: EN, enzymology
Thermotoga maritima: GE, genetics
alpha-Glucosidases: GE, genetics
*alpha-Glucosidases: IP, isolation & purification
*alpha-Glucosidases: ME, metabolism

CAS REGISTRY NO.: 3483-12-3 (Dithiothreitol); 53-84-9 (NAD); 7439-96-5 (Manganese)

CHEMICAL NAME: 0 (Cations, Divalent); 0 (Recombinant Proteins); 0 (Sulfhydryl Compounds); EC 3.2.1.20 (alpha-Glucosidases)

L156 ANSWER 7 OF 18 MEDLINE on STN

ACCESSION NUMBER: 1998166175 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 9505277

TITLE: Recombinant human acid alpha-glucosidase corrects acid

alpha-glucosidase-deficient human fibroblasts, quail fibroblasts, and quail myoblasts.

AUTHOR: Yang H W; Kikuchi T; Hagiwara Y; Mizutani M; Chen Y T; Van Hove J L

CORPORATE SOURCE: Department of Pediatrics, Duke University Medical Center, Durham, North Carolina 27710, USA.

SOURCE: Pediatric research, (1998 Mar) Vol. 43, No. 3, pp. 374-80. Journal code: 0100714. ISSN: 0031-3998. L-ISSN: 0031-3998.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199805

ENTRY DATE: Entered STN: 14 May 1998
Last Updated on STN: 3 Mar 2000
Entered Medline: 1 May 1998

ABSTRACT:
Acid alpha-glucosidase (GAA) deficiency causes Pompe disease, a lethal lysosomal glycogen storage disease for which no effective treatment currently exists. We investigated the endocytic process in deficient cells of human recombinant GAA produced in Chinese hamster ovary cells, and the potential of GAA-deficient Japanese acid maltase-deficient quail as a model for evaluating the enzyme replacement therapy for Pompe disease. After 24-h incubation with a single dose of recombinant enzyme, intracellular GAA and glycogen levels in deficient human fibroblasts were normalized, and this correction lasted for 7 d. The 110-kD precursor recombinant enzyme was processed to the 76-kD mature form within 24 h after uptake. Intracellular GAA levels in deficient quail fibroblasts and myoblasts were similarly corrected to their average normal levels within 24 h. Differences existed in the efficiency of endocytosis among subfractions of the enzyme, and among different cell types. Fractions with a larger proportion of precursor GAA were endocytosed more efficiently. Quail fibroblasts required a higher dose, 4200 nmol.h-1.mL-1 to normalize intracellular GAA levels than human fibroblasts, 1290 nmol.h-1.mL-1, whereas primary quail myoblasts required 2800 nmol.h-1.mL-1. In all three cell lines, the endocytosed enzyme localized to the lysosomes on immunofluorescence staining, and the endocytosis was inhibited by mannose 6-phosphate (Man-6-P) added to the culture medium. Despite structural differences in Man-6-P receptors between birds and mammals, these studies illustrate that Man-6-P receptor mediated endocytosis is present in quail muscle cells, and demonstrate the potential of acid maltase-deficient quail to test receptor mediated enzyme replacement therapy for Pompe disease.

CONTROLLED TERM: Animals
Biological Transport, Active
CHO Cells
Cells, Cultured
Cricetinae
Disease Models, Animal
Endocytosis
Fibroblasts: DE, drug effects
Fibroblasts: EN, enzymology
Glucan 1,4-alpha-Glucosidase: AD, administration & dosage
*Glucan 1,4-alpha-Glucosidase: DF, deficiency
*Glucan 1,4-alpha-Glucosidase: PD, pharmacology
Glycogen: ME, metabolism
*Glycogen Storage Disease Type II: DT, drug therapy
*Glycogen Storage Disease Type II: EN, enzymology
Glycogen Storage Disease Type II: ME, metabolism
Humans
Kinetics

Muscles: CY, cytology
Muscles: DE, drug effects
Quail
Receptor, IGF Type 2: ME, metabolism
Recombinant Proteins: AD, administration & dosage
Recombinant Proteins: PD, pharmacology
alpha-Glucosidases

CAS REGISTRY NO.: 9005-79-2 (Glycogen)
CHEMICAL NAME: 0 (Receptor, IGF Type 2); 0 (Recombinant Proteins); EC 3.2.1.20 (alpha-Glucosidases); EC 3.2.1.3 (Glucan 1,4-alpha-Glucosidase)

L156 ANSWER 8 OF 18 MEDLINE on STN
ACCESSION NUMBER: 1997378221 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9234902
TITLE: Sequencing of N-linked oligosaccharides directly from protein gels: in-gel deglycosylation followed by matrix-assisted laser desorption/ionization mass spectrometry and normal-phase high-performance liquid chromatography.
AUTHOR: Kuster B; Wheeler S F; Hunter A P; Dwek R A; Harvey D J
CORPORATE SOURCE: Department of Biochemistry, Oxford Glycobiology Institute, University of Oxford, United Kingdom.
SOURCE: Analytical biochemistry, (1997 Jul 15) Vol. 250, No. 1, pp. 82-101.
Journal code: 0370535. ISSN: 0003-2697. L-ISSN: 0003-2697.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 16 Sep 1997
Last Updated on STN: 29 Jan 1999
Entered Medline: 4 Sep 1997

ABSTRACT:
A generally applicable, rapid, and sensitive method for profiling and sequencing of glycoprotein-associated N-linked oligosaccharides from protein gels was developed. The method employed sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) for protein separation and purification and in-gel deglycosylation using PNGase F for glycan release. Profiles of the neutral glycans from bovine ribonuclease B, chicken ovalbumin, and human immunoglobulin G (IgG), as well as sialic acid-containing sugars (following esterification of the acidic groups) of bovine fetuin and bovine alpha1-acid glycoprotein, were obtained by matrix-assisted laser desorption/ionization mass spectrometry (MALDI MS) and by normal-phase high-performance liquid chromatography following fluorescent labeling. Oligosaccharides were sequenced using specific exoglycosidases, and digestion products were analyzed by MALDI MS. Between 50 and 100 pmol (1.5 to 15 microg) of glycoprotein applied to the gel was sufficient to characterize its oligosaccharide contents. The identity of all glycoproteins investigated could be confirmed after deglycosylation by in-gel trypsin treatment followed by MALDI MS mass mapping and matching the measured molecular weights to a sequence database. The technique was used for the characterization of the glycan moieties of human immunodeficiency virus recombinant gp120 (Chinese hamster ovary cells) and to monitor changes in the glycosylation of this glycoprotein when produced in the presence of a glucosidase I inhibitor. Furthermore, since heavy and light chains of IgG became separated by SDS-PAGE, it could be established that most glycans were associated with the heavy chains.
CONTROLLED TERM: 1-Deoxynojirimycin: AA, analogs & derivatives

1-Deoxynojirimycin: PD, pharmacology
Amidohydrolases
Animals
Antiviral Agents: PD, pharmacology
CHO Cells
Carbohydrate Sequence
Chromatography, High Pressure Liquid
Cricetinae
Electrophoresis, Polyacrylamide Gel
Enzyme Inhibitors: PD, pharmacology
*Glycoproteins: AN, analysis
Glycoproteins: IP, isolation & purification
Glycoside Hydrolases
HIV Envelope Protein gp120: AN, analysis
HIV-1
Humans
Immunoglobulin G: AN, analysis
Molecular Sequence Data
*Oligosaccharides: AN, analysis
Oligosaccharides: IP, isolation & purification
Peptide-N4-(N-acetyl-beta-glucosaminyl) Asparagine Amidase
Recombinant Proteins: AN, analysis
Sensitivity and Specificity
Spectrometry, Mass, Matrix-Assisted Laser Desorption-Ionization
alpha-Glucosidases: AI, antagonists & inhibitors

CAS REGISTRY NO.: 19130-96-2 (1-Deoxynojirimycin)

CHEMICAL NAME: 0 (Antiviral Agents); 0 (Enzyme Inhibitors); 0 (Glycoproteins); 0 (HIV Envelope Protein gp120); 0 (Immunoglobulin G); 0 (Oligosaccharides); 0 (Recombinant Proteins); 0 (miglustat); EC 3.2.1.- (Glycoside Hydrolases); EC 3.2.1.- (glucosidase I); EC 3.2.1.20 (alpha-Glucosidases); EC 3.5.- (Amidohydrolases); EC 3.5.1.52 (Peptide-N4-(N-acetyl-beta-glucosaminyl) Asparagine Amidase)

L156 ANSWER 9 OF 18 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2006:437095 HCAPLUS Full-text
DOCUMENT NUMBER: 144:449073
TITLE: Gene expression profiling of monocytes in diagnosis of leukemias associated with chromosomal translocations and selection of therapies
INVENTOR(S): Haferlach, Torsten; Dugas, Martin; Kern, Wolfgang; Kohlmann, Alexander; Schnittger, Susanne; Schoch, Claudia
PATENT ASSIGNEE(S): Roche Diagnostics G.m.b.H., Germany; F.Hoffmann-La Roche A.-G.
SOURCE: PCT Int. Appl., 329 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006048270	A2	20060511	WO 2005-EP11741	20051103

WO 2006048270 A3 20060720

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2004-625697P P 20041104

AB Genes showing changes in levels of expression in monocytes in different forms of leukemia compared to healthy monocytes are identified for use in the rapid diagnosis of the disease and in identification of subtypes that will respond well to certain therapies. In addition to methods of genotyping leukemia, the invention also provides related kits and systems.

CC 14-1 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 3

IT Calmodulins
Synaptobrevins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(1, gene for, in diagnosis of leukemias; gene expression profiling of monocytes in diagnosis of leukemias associated with chromosomal translocations and selection of therapies)

IT Gene, animal
RL: ANT (Analyte); DGN (Diagnostic use); PRP (Properties); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(ARHU, in diagnosis of leukemias; gene expression profiling of monocytes in diagnosis of leukemias associated with chromosomal translocations and selection of therapies)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p75NTR-associated cell death executor, gene for, in diagnosis of leukemias; gene expression profiling of monocytes in diagnosis of leukemias associated with chromosomal translocations and selection of therapies)

IT 9000-86-6, Glutamic pyruvate transaminase 9000-95-7, Ectonucleoside triphosphate diphosphohydrolase 9001-80-3, Phosphofructokinase 9001-84-7, Phospholipase A2 9003-99-0, Myeloperoxidase 9004-06-2, Neutrophil elastase 9013-18-7, Long-chain CoA ligase 9013-75-6, Histidine ammonia-lyase 9014-48-6, Transketolase 9023-64-7, Glutamate-cysteine ligase 9024-78-6, Kynureninase 9025-35-8 9025-62-1, Arylsulfatase C 9026-43-1 9026-93-1, Adenosine deaminase 9027-67-2, Terminal deoxynucleotidyltransferase 9028-56-2, 3-α Hydroxysteroid dehydrogenase 9030-45-9, Glutamine-fructose-6-phosphate transaminase 9032-67-1, Dipeptidylpeptidase 9032-95-5 9033-27-6, Isopentenyl-diphosphate Δ isomerase 9036-21-9, Phosphodiesterase 4 9040-75-9, Monoglyceride lipase 9041-92-3, α-1 Antiproteinase 9054-65-3, Branched chain aminotransferase 9068-78-4, Histidyl-tRNA synthetase 9074-87-7, γ-Glutamyl hydrolase 9075-15-4, UDP-N-acetyl-α-D-galactosamine:protein N-acetylgalactosaminyltransferase 11016-39-0, Properdin 12651-27-3, Transcobalamin I 37211-76-0, Asparaginyl-tRNA synthetase 37213-56-2, (Adipsin) 37289-41-1, Sulfamidase 39279-34-0, α-1,3-Fucosyltransferase 50812-37-8, Glutathione S transferase

52227-79-9, Prostaglandin E synthase 56645-49-9, Cathepsin G 60382-71-0, Diacylglycerol kinase 61970-06-7, Methylthioadenosine phosphorylase 65666-34-4, Glucosamine 6-sulfatase 70248-65-6, Methionine sulfoxide reductase 71965-46-3, Cathepsin S 80619-02-9, Arachidonate 5-lipoxygenase 86498-16-0, UDP-N-acetylglucosamine:α1,3-D-mannoside β-1,4-N-acetylglucosaminyltransferase 90119-07-6, Leukotriene A4 hydrolase 93928-65-5, Aminoadipate-semialdehyde synthase 103220-14-0, Corticostatin 107544-29-6, Cystatin A 110277-64-0, Acyloxyacyl hydrolase 115926-52-8, Phosphoinositide-3-kinase 122191-40-6, Caspase 1 123644-75-7, Dimethylarginine dimethylaminohydrolase 127464-60-2, Vascular endothelial growth factor 130731-20-3, Isoprenylcysteine carboxyl methyltransferase 137367-20-5, Leukotriene B4 12-hydroxydehydrogenase 139316-54-4, Granulin 142008-29-5, CAMP-dependent protein kinase 145539-86-2, HCK kinase 146480-36-6, Matrix metalloproteinase 9 147230-71-5, FMS-related tyrosine kinase 3 156859-16-4, Gene RYK tyrosine kinase 158254-85-4, Lysophosphatidic acid phosphatase 161384-20-9, Protein kinase Cν 168680-17-9, Interleukin receptor-associated kinase 3 170006-50-5, Cathelicidin 184049-62-5, Dual specificity phosphatase 6 189303-50-2, Cathepsin W 191359-14-5, MAP kinase-interacting serinethreonine kinase 2 193099-10-4, Metargidin 194554-71-7, Tissue factor pathway inhibitor 196717-71-2, Epiregulin 198154-07-3, Cystatin F 199876-57-8, Mitogen-activated protein kinase kinase kinase kinase 2 203810-04-2, Protein kinase MRCKα 203810-05-3, Protein kinase MRCKβ 252349-85-2, Cyritestin 1 252351-00-1, Metalloproteinase ADAM8 252852-50-9, SUMO-specific protease 285571-90-6, NIMA-related kinase 6 330469-70-0, Azurocidin 333425-95-9, Protein kinase D2 362674-81-5, Protein phosphatase 2 475678-93-4, Short-chain dehydrogenase reductase 488850-98-2, Protein kinase Cε 644990-12-5, Peroxiredoxin 1 657407-83-5, Calpain 3 866622-31-3, Prokineticin 2

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene for, in diagnosis of leukemias; gene expression profiling of monocytes in diagnosis of leukemias associated with chromosomal translocations and selection of therapies)

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L156 ANSWER 10 OF 18 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2005:238412 HCAPLUS Full-text
DOCUMENT NUMBER: 142:291405
TITLE: Coupling of mannopyranosyl oligosaccharide containing mannose-6-phosphate (M6P) or other oligosaccharides bearing other terminal hexoses to carbonyl groups on oxidized lysosomal enzymes for treating lysosomal storage disease
INVENTOR(S): Zhu, Yunxiang
PATENT ASSIGNEE(S): Genzyme Corporation, USA
SOURCE: U.S. Pat. Appl. Publ., 33 pp., Cont.-in-part of U.S. Ser. No. 51,711.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

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     US 20050058634       A1     20050317    US 2004-943893          20040920
     US 7723296           B2     20100525
     US 20020137125       A1     20020926    US 2002-51711           20020117
     US 7001994           B2     20060221
PRIORITY APPLN. INFO.:                       US 2001-263078P     P  20010118
                                             US 2002-51711       A2 20020117
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
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AB Methods to introduce highly phosphorylated mannopyranosyl oligosaccharide derivs. containing mannose-6-phosphate (M6P), or other oligosaccharides bearing other terminal hexoses, to carbonyl groups on oxidized glycans of glycoproteins while retaining their biol. activity are described. The methods are useful for modifying glycoproteins, including those produced by recombinant protein expression systems, to increase uptake by cell surface receptor-mediated mechanisms, thus improving their therapeutic efficacy in a variety of applications. Conjugation of phosphopentamannose-hydrazine to β-glucuronidase does not inactivate the enzyme. Chemical conjugating M6P-containing oligosaccharides onto recombinant human α-glucosidase (rhGAA) did not affect its enzymic activity. Conjugation of mono- and bis-phosphorylated oligomannose residues onto rhGAA improved its binding to CI-MPR (cation-independent mannose-6-phosphate receptor) and improved its uptake into cells in vitro. Modifying rhGAA with bis-M6P hydrazide resulted in a significant improvement in glycogen clearance in old and young pompe mice.

IC ICM A61K038-47
ICS C12N009-10
INCL 424094610
CC 1-10 (Pharmacology)

IT Mannose receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(mannose 6-phosphate; coupling of mannose-6-phosphate and other oligosaccharides to lysosomal enzymes for treating lysosomal storage disease)

IT Hexoses
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(phosphorylated; coupling of mannopyranosyl oligosaccharide containing mannose-6-phosphate (M6P) or other oligosaccharides bearing other terminal hexoses to carbonyl groups on oxidized lysosomal enzymes for treating lysosomal storage disease)

IT 9001-42-7 9001-45-0 9012-33-3, β-N-Acetyl-hexosaminidase
9025-35-8, α Galactosidase A
37228-64-1, β Glucocerebrosidase 37288-40-7,
α-N-Acetylglucosaminidase
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coupling of mannose-6-phosphate and other oligosaccharides to lysosomal enzymes for treating lysosomal storage disease)

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OS.CITING REF COUNT:      4     THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD
                                (4 CITINGS)
REFERENCE COUNT:          97    THERE ARE 97 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
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L156 ANSWER 11 OF 18 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2005:671727 HCAPLUS Full-text
DOCUMENT NUMBER: 143:166667
TITLE: The curcuminoids- and anthocyanins-responsive genes in human adipocytes and their use in screenings of anti-obesity and anti-diabetes drugs

INVENTOR(S): Ueno, Yuki; Tsuda, Takanori; Takanori, Hitoshi; Yoshikawa, Toshikazu; Osawa, Toshihiko
PATENT ASSIGNEE(S): Biomarker Science Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 85 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
JP 2005198640	A	20050728	JP 2004-53258		20040227
PRIORITY APPLN. INFO.:			JP 2003-394758	A	20031125

AB The curcuminoids- and anthocyanins-responsive gene expression profiles in adipocytes have been revealed. The curcuminoids- and anthocyanins-responsive genes are designed to be used as the index markers in the screenings of the substances that can affect the gene expression patterns in obesity and diabetes. These substances can be the candidates of anti-obesity and anti-diabetes drugs. Therefore, the groups of curcuminoids- and anthocyanins-responsive genes are intended to be used as markers in a form of kit such as DNA chip for the screening of anti-obesity and anti-diabetes drugs.

IC ICM C12N005-02
ICS C12N015-09; C12Q001-68

CC 1-10 (Pharmacology)
Section cross-reference(s): 2, 3, 6, 7, 9, 14

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ligand-binding, mannose 6 phosphate receptor binding protein, gene for; curcuminoids- and anthocyanins-responsive genes in human adipocytes and their use in screenings of anti-obesity and anti-diabetes drugs)

IT 152415-21-9, Transcription factor EF1 (Rattus subunit A) 162079-88-1, Reductase, carbonyl (reduced nicotinamide adenine dinucleotide phosphate) (Rattus norvegicus strain Sprague-Dawley WBC gene Cbr) 171042-38-9, Protein (rat gene Tsc2) 172728-38-0, Cholesterol esterase (Rattus norvegicus strain Sprague-Dawley) 177571-86-7, Kinase (phosphorylating), mitogen-activated protein kinase kinase (Rattus norvegicus gene MEKK1) 178605-25-9 178862-53-8, Dihydropyrimidinase (Rattus norvegicus) 180032-55-7, Synthetase, acyl coenzyme A (Rattus norvegicus strain Wistar clone pBACS II isoenzyme 3) 180789-02-0, Proline rich protein (Rattus norvegicus strain Sprague-Dawley clone cc4) 182022-39-5, Heat shock protein 27 (Rattus norvegicus strain Fisher gene Hsp27) 184379-51-9 188204-81-1 189235-72-1 189642-68-0 190977-39-0 195160-50-0, Molecular chaperone GroES (Rattus norvegicus strain Wistar/Sprague-Dawley gene CPN10) 195160-51-1, Molecular chaperone GroEL (Rattus norvegicus strain Wistar/Sprague-Dawley gene Hsp60) 195264-17-6, Transport protein NRAMP2 (natural resistance-associated macrophage protein 2) (Rattus norvegicus strain Sprague-Dawley gene Nramp2) 196967-94-9 199810-33-8 202669-75-8 204659-52-9 206076-49-5 208734-68-3 209119-04-0, Protein (Rattus norvegicus strain Sprague-Dawley gene RDJ1 molecular chaperone DnaJ sequence homolog) 209408-53-7 210229-37-1 212510-87-7 212510-88-8 212568-39-3 212900-59-9 213260-09-4 213538-94-4 213539-39-0 213762-56-2, Transcription factor (Rattus norvegicus gene SNURF small nuclear RING finger) 214909-94-1 214910-30-2, Transport protein chloride-potassium-sodium cotransporter (Rattus norvegicus strain Wistar gene Nkcc1) 215028-81-2 215171-49-6 215518-56-2, Protein (Rattus norvegicus gene DPM2) 216147-98-7, Protein Grb14 (Rattus norvegicus) 216971-93-6, Protein (Rattus norvegicus gene RGC-32) 219678-51-0

219678-52-1 220163-76-8, GABAB receptor (Rattus norvegicus clone GABABR1c) 220895-50-1, Phosphatase, protein phosphoserine/phosphothreonine, 2C (Rattus norvegicus clone 6 gene PP2Cδ isoenzyme δ) 226893-93-2, Cytocentrin (rat clone pBSCC47) 239087-54-8 240407-65-2, Cytidylyltransferase, phosphatidate (Rattus norvegicus strain Wistar) 240407-72-1 243658-17-5 245509-90-4 246224-57-7, DNA-binding protein MARBP (MAR DNA binding protein) (Rattus N-terminal fragment) 248250-31-9, Transcription factor HNF1β (hepatocyte nuclear factor 1β) (Rattus norvegicus gene NF1-B) 255811-00-8 260425-82-9, Vesicle associated protein 1 (Rattus norvegicus gene VAP1) 266302-37-8 282122-00-3, Sulfonylurea receptor 2B (Rattus norvegicus) 329337-98-6 336652-08-5 459500-15-3, GenBank AAB06202 459503-23-2, GenBank CAA70512 459503-43-6, GenBank AAB67042 459503-71-0, GenBank CAA69642 459505-25-0, GenBank AAA79137 459527-07-2, GenBank AAA19241 459578-77-9, GenBank AAC69605 459581-24-9, GenBank CAA67711 459584-35-1, GenBank CAA61843 459638-61-0, GenBank AAC71014 459639-82-8, GenBank AAC77910 459640-23-4, GenBank AAC83801 462179-66-4 462232-78-6 462233-54-1 462261-56-9 462282-92-4 462285-02-5, Protein Sec7B (Rattus norvegicus) 462321-44-4 462321-45-5 477481-96-2 477984-61-5, Binding protein (Rattus norvegicus syntaxin binding protein Munc18-2) 479793-76-5 479793-77-6 479793-78-7 479793-79-8 479793-80-1 479793-81-2 479793-82-3 479793-83-4 479793-84-5 479793-85-6 483110-98-1, Syntaxin 5 (Rattus norvegicus) 483112-64-7 483113-00-4 483114-35-8 483115-45-3 483120-91-8 483120-93-0 483121-05-7 483126-04-1 483183-26-2 483183-61-5 483184-66-3 483185-34-8 483185-66-6 483186-07-8 483186-19-2, Catalase (Rattus norvegicus) 483189-50-0 483191-42-0 483191-62-4 483191-68-0 483192-54-7 483193-76-6 483195-89-7 483196-72-1 483197-01-9 483198-23-8 483198-85-2 483198-93-2 483199-37-7 483200-26-6 483200-60-8 483201-16-7 483201-23-6 483201-38-3 483201-64-5, Phospholipase C (Rattus isoenzyme III) 483202-20-6 483202-46-6 483203-42-5 483203-79-8, Ras protein c-ras (Rattus norvegicus) 483203-95-8, Retinol-binding protein (Rattus C-terminal fragment) 483204-14-4 483206-70-8 483207-09-6 483207-88-1, Transferrin receptor (Rattus norvegicus gene transferrin receptor C-terminal fragment) 483208-56-6, Thyrotropin receptor (rat precursor) 483208-77-1 483208-85-1 483210-89-5 483211-12-7 483228-10-0 483228-80-4 483230-84-8 483230-86-0 483231-42-1 483232-06-0 483235-06-9 483462-38-0 483464-33-1, Protein (Rattus norvegicus clone lambda 4A1-3. open reading frame orfa' 268-amino acid) 483464-35-3, Protein (Rattus norvegicus clone lambda 4A1-3. open reading frame orfa 259-amino acid) 483464-38-6, Protein (Rattus norvegicus clone lambda 4A1-3. open reading frame orfb 336-amino acid) 483464-40-0, Protein (Rattus norvegicus clone lambda 4A1-3. open reading frame orfc 135-amino acid) 483464-42-2, Protein (Rattus norvegicus clone lambda 4A1-3. open reading frame orfd1 276-amino acid) 483464-44-4, Protein (Rattus norvegicus clone lambda 4A1-3. open reading frame orfd2 367-amino acid) 483472-43-1 483474-03-9 483474-11-9 483474-71-1 483475-31-6 483475-38-3, Cytochrome P 450 1B1 (Rattus norvegicus strain Sprague-Dawley gene CYP1B1) 483475-88-3 483479-76-1 483480-98-4 483481-86-3 483489-66-3 483489-76-5 483490-15-9 483490-23-9 483490-24-0 483493-72-7 483495-09-6 483498-33-5 483498-75-5 483499-19-0 483509-08-6 483513-51-5 483513-52-6 483518-69-0 483530-43-4, Protein PMF31 (Rattus norvegicus strain Wistar) 483532-13-4 483536-41-0 483544-29-2 483544-36-1 483545-44-4 483545-79-5, Prostacyclin receptor (Rattus clone 12) 483545-95-5 483546-54-9 483546-55-0 483546-75-4 483547-56-4 483552-14-3, Cyclin D2 (Rattus norvegicus clone Nb2) 483552-92-7 483553-62-4 483553-79-3, Kinase (phosphorylating), phosphatidylinositol 4- (Rattus norvegicus strain Wister Imamichi) 483553-87-3 483554-45-6 483555-95-9

483556-91-8 483558-40-3 483560-06-1 483560-10-7 483561-46-2 483561-59-7 483561-60-0 483561-61-1 483561-76-8 483562-06-7 483563-37-7 483563-71-9 483564-89-2 483565-73-7 483567-12-0 483567-83-5, Phosphatase, phosphoprotein (Rattus isoenzyme 2C2) 483569-48-8 483570-54-3 483571-70-6 483572-34-5 483572-40-3 483576-01-8 483576-08-5, Prostanoid receptor type FP (Rattus) 483576-12-1 483576-63-2 483579-70-0 483581-35-7, Kinase (phosphorylating), protein, ROKα (Rattus norvegicus) 483583-15-9, GenBank AAB39620 483584-53-8 483590-18-7 483590-72-3 483592-39-8 483593-57-3 483596-31-2 483597-43-9 483604-59-7 483605-84-1 483606-73-1, Spinophilin (Rattus norvegicus) 483607-78-9
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; curcuminoids- and anthocyanins-responsive genes in human adipocytes and their use in screenings of anti-obesity and anti-diabetes drugs)

IT 9000-97-9 9001-16-5, Cytochrome c oxidase 9001-39-2, Glucose-6-phosphatase 9001-51-8, Hexokinase 9001-53-0, Amine oxidase, copper containing 9001-67-6, Sialidase 9001-80-3, Phosphofructokinase 9004-06-2, Matrix metalloproteinase 12 9013-02-9, Adenylate kinase 9013-08-5, Phosphoenolpyruvate carboxykinase 9013-10-9, Glucosamine-6-phosphate isomerase 9014-18-0, Nicotinamide nucleotide transhydrogenase 9014-42-0, Proteoglycan 4 9023-62-5, Glutathione synthetase 9023-69-2, Asparagine synthetase 9023-93-2, Acetyl-Coenzyme A carboxylase 9025-24-5, Carboxypeptidase B 9025-26-7, Cathepsin D 9025-32-5 9025-35-8 9025-42-7 9025-73-4, Phosphoserine phosphatase 9026-04-4, Thiosulfate sulfurtransferase 9026-05-5, Mercaptopyruvate sulfurtransferase 9026-23-7, Carbamoyl-phosphate synthetase 9026-42-0, Pyridoxal kinase 9026-84-0, Ribokinase 9027-01-4 9027-13-8, Enoyl-Coenzyme A hydratase 9027-56-9, Acetylglucosaminidase 9027-72-9, Adenosine kinase 9029-12-3, Glutamate dehydrogenase 1 9029-14-5, Methylenetetrahydrofolate dehydrogenase 9029-61-2, Kynurenine 3-monooxygenase 9029-62-3, Squalene epoxidase 9029-78-1, Betaine-homocysteine methyltransferase 9029-80-5, Histamine methyltransferase 9029-90-7, Carnitine acetyltransferase 9029-95-2, Glycine acyltransferase 9030-22-2, Uridine phosphorylase 9030-23-3, Platelet-derived endothelial cell growth factor 9030-27-7, Proteins, pre-B cell colony-enhancing factor 9030-87-9, Hydroxyprostaglandin dehydrogenase 15 9030-90-4, Phosphoserine aminotransferase 9030-96-0, Isoleucine-tRNA synthetase 9031-11-2, Lactase 9031-41-8, Leucyl/cystinyl aminopeptidase 9031-61-2, Thymidylate synthetase 9031-70-3, Dipeptidyl peptidase VI 9031-86-1, Aspartoacylase 9032-25-1, Cytochrome b5 reductase 9032-64-8, Nucleotide pyrophosphohydrolase 9033-07-2, Glycosyltransferase 9033-23-2 9035-39-6, Cytochrome b5 9036-21-9, CAMP phosphodiesterase 9036-37-7, δ-Aminolevulinate dehydratase 9036-43-5, Steroid-5α-reductase 9039-53-6, Urokinase 9040-08-8, 20-α (3-α)-Hydroxysteroid dehydrogenase 9041-92-3, α1-Antiproteinase 9054-51-7, Monocytic leukemia zinc finger protein-related factor 9074-10-6, Biliverdin reductase 9075-64-3, Angiotensinase C 11002-13-4, Angiotensinogen 37184-63-7 37213-56-2, Adipsin 37228-65-2, Sarcosine dehydrogenase 37256-25-0, Formyltetrahydrofolate dehydrogenase 37257-21-9, Glutaminyl-peptide cyclotransferase 37278-34-5, Heparan sulfate sulfotransferase 37278-45-8, 6-Phosphogluconolactonase 37290-66-7, Sialic acid synthase 39346-44-6 50864-48-7, Sphingosine kinase 1 51845-53-5, Myosin light chain kinase 51901-16-7, 1-Acylglycerol-3-phosphate O-acyltransferase 60202-07-5, Cholesterol 25-hydroxylase 60382-71-0, Diacylglycerol kinase 60529-76-2, Thymopoietin 61970-06-7, Methylthioadenosine phosphorylase

62213-44-9, Dolichyl-phosphate mannosyltransferase 63551-76-8, Phospholipase C, γ 71124-51-1, β-Galactoside α-2,3-sialyltransferase 74506-58-4, Galactosaminoglycan uronyl-2-sulfotransferase 75922-89-3, Pyrroline-5-carboxylate synthetase 76901-00-3, Platelet-activating factor acetylhydrolase 79955-99-0, Matrix metalloproteinase 3 80146-85-6 82391-38-6, Branched chain α-ketoacid dehydrogenase kinase 86480-67-3, Ubiquitin thiolesterase 86551-03-3, Electron-transferring-flavoprotein dehydrogenase 90698-26-3, Ribosomal protein S6 kinase 93928-65-5, Aminoadipic semialdehyde synthase 96231-41-3, β-Inhibin 96779-46-3, Mephenytoin 4-hydroxylase 97089-82-2, 6-Pyruvoyltetrahydropterin synthase 103106-89-4, α-Inhibin 104625-48-1, Activin A 105238-46-8, Macropain 105913-04-0 106640-75-9, Aldo-keto reductase 106956-32-5, Oncostatin M 109489-77-2, Tetranectin 111693-80-2, Inositol polyphosphate-4-phosphatase 114949-23-4, Activin A-B 116036-67-0, Cytidine monophosphate-N-acetylneuraminic acid hydroxylase 122653-71-8, Adrenergic receptor 2 kinase 125752-90-1, GM3 synthase 139639-23-9, Tissue plasminogen activator 141467-21-2, Calcium/calmodulin-dependent protein kinase I 142805-56-9, DNA topoisomerase II 143180-75-0, DNA topoisomerase I 145809-21-8, Tissue inhibitor of metalloproteinase 3 146838-30-4, Mitogen-activated protein kinase-activated protein kinase 2 147014-96-8, Cyclin-dependent kinase 5 147171-38-8, CDC-like kinase 1 150316-07-7, Mitogen-activated protein kinase kinase kinase 8 151769-16-3, Tumor necrosis factor α converting enzyme 153700-57-3, G Protein-coupled receptor kinase 5 155807-64-0, Flap structure-specific endonuclease 1 160477-63-4, Tissue factor pathway inhibitor 2 161384-20-9, Protein kinase C μ 167397-96-8, Interleukin-1 receptor kinase 169494-85-3, Leptin 170347-50-9, FAST kinase 172308-13-3, Mitogen-activated protein kinase kinase 3 172521-75-4, Relaxin 2 176023-64-6, Mitogen-activated protein kinase 12 182372-13-0, Rho protein kinase 182762-08-9, Caspase 4 185915-22-4, Fibroblast growth factor 13 186003-84-9 187414-15-9, Cystatin M 188417-84-7, Vascular endothelial growth factor C 189460-40-0, Connective tissue growth factor 191359-13-4, MAP kinase-interacting serine/threonine kinase 1 193363-12-1, Vascular endothelial growth factor D 193830-08-9, Cartilage-derived morphogenetic protein-1 196717-99-4, Prenylcysteine lyase 214210-47-6, Neuropilin 1 219575-48-1, STE20-like protein kinase 241475-96-7, Matriptase 241824-56-6, Death-associated protein kinase 2 244292-73-7, Corin (enzyme) 252901-99-8, Tousled-like kinase 2 252902-02-6, Homeodomain interacting protein kinase 2 289899-93-0, Mitogen-activated protein kinase 9 289905-84-6, Dual specificity protein phosphatase 3 294190-69-5, T-LAK cell-originated protein kinase 300857-98-1, Protein tyrosine phosphatase, receptor type, F 324751-96-4, Stanniocalcin 2 324752-01-4, Stanniocalcin 1 330197-29-0, Cyclin-dependent kinase 7 335605-46-4, Mitogen-activated protein kinase kinase 7 354123-54-9, Serine/threonine kinase 17a 360565-62-4, Mitogen-activated protein kinase phosphatase x 370088-29-2, Mitogen-activated protein kinase kinase kinase kinase 4 371761-91-0, Survivin 400653-73-8, Dual specificity phosphatase 5 404843-77-2, Reelin 458560-40-2, Serine/threonine protein kinase 6 475678-93-4, WW domain containing oxidoreductase 476196-08-4, Calcium/calmodulin-dependent protein kinase IV 644990-12-5, Peroxiredoxin 1 657407-83-5, Calpain 3 767341-03-7, Hypocretin

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene for; curcuminoids- and anthocyanins-responsive genes in human adipocytes and their use in screenings of anti-obesity and anti-diabetes drugs)

IT 138362-96-6 139821-50-4 139821-55-9 139822-40-5 139823-85-1 139826-39-4 139847-64-6, DNA (Rattus proteinase inhibitor calpastatin cDNA plus flanks) 139849-17-5 139858-50-7, DNA (Rattus norvegicus strain Sprague-Dawley gene cEH epoxide hydratase C-terminal fragment specifying cDNA plus 3'-flank) 139859-10-2, DNA (Rattus norvegicus kinesin light chain C cDNA) 139860-60-9, DNA (Rattus rattus strain Sprague-Dawley clone pαRL3 α-crystallin B-chain cDNA plus flanks) 140007-75-6 140044-67-3 140044-92-4, DNA (rat liver gene Cebp) 140044-95-7, DNA (Rattus rattus clone PC 12 transcription factor c-fos cDNA plus flanks) 140045-50-7 140045-80-3 140045-88-1, DNA (Rattus norvegicus γ-glutamylcysteine synthetase cDNA plus flanks) 140046-30-6 140046-60-2 140046-78-2 140046-85-1 140046-89-5 140047-19-4 140047-69-4, DNA (Rattus norvegicus strain Sprague-Dawley gene PRKCγ plus flanks) 140047-72-9 140047-78-5 140047-83-2 140048-01-7 140048-09-5, DNA (Rattus norvegicus strain Sprague-Dawley clone R-II-51 protein kinase (phosphorylating) A type II isoenzyme regulatory subunit C-terminal fragment specifying cDNA) 140048-70-0 140050-76-6, DNA (Rattus norvegicus protein O-methyltransferase cDNA plus flanks) 140063-22-5 140066-83-7 140072-23-7 140085-01-4 140104-42-3 140298-86-8 140299-22-5 140299-37-2 140299-53-2, GenBank M31176 140299-60-1 140299-67-8 140299-89-4 140301-00-4, DNA (Rattus norvegicus potassium-sodium-dependent adenosine triphosphatase subunit α cDNA plus flanks) 140301-05-9 140301-48-0 140302-00-7 140302-57-4 140302-90-5 140303-29-3 140316-93-4 140326-64-3 140334-58-3, DNA (Rattus rattus strain Wistar myosin light chain cDNA plus flanks) 140352-89-2, DNA (Rattus norvegicus strain Fisher gene Hsp27 heat-shock protein HSP 27 cDNA plus flanks) 140358-12-9, DNA (Rattus norvegicus strain Fischer Copenhagen high-mobility group protein cDNA 3'-UTR fragment) 140535-47-3 140535-79-1 140536-60-3 140731-42-6, DNA (Rattus norvegicus strain Sprague-Dawley mitochondria gene COXI plus gene COXII plus open reading frame orfa6 gene plus ATPase gene plus gene COXIII plus open reading frame orf3 plus open reading frame orf41 plus open reading frame orf4 plus open reading frame orf5 fragment) 140770-01-0, DNA (Rattus norvegicus clone lambda 4A1-3 open reading frame orfa' plus open reading frame orfa plus open reading frame orfb plus open reading frame orfc plus open reading frame orfd1 plus open reading frame orf d2 plus flanks) 140770-31-6, DNA (Rattus norvegicus strain Buffalo gene c-myc plus flanks) 140772-99-2 140787-25-3 140795-40-0 140801-58-7 140810-28-2 140832-84-4, DNA (Rattus norvegicus gene GLUR4 glutamate receptor cDNA plus flanks) 141000-10-4, DNA (rat clone 37A/7B gene ALR plus flanks) 141006-31-7 141165-09-5 142098-65-5, DNA (Rattus norvegicus strain Sprague-Dawley gene CaM-PDE clone Arb5 cyclic 3',5'-nucleotide phosphodiesterase calmodulin-dependent 63-kilodalton isoenzyme cDNA plus flanks) 142258-88-6, DNA (Rattus norvegicus strain Wistar multicatalytic proteinase subunit C2 cDNA plus flanks) 142317-57-5 143343-25-3, DNA (Rattus norvegicus strain Sprague-Dawley transcription factor Sp1 cDNA plus flanks) 143343-26-4, DNA (Rattus norvegicus strain Sprague-Dawley transcription factor BTEB (BTE binding protein) cDNA plus flanks) 143561-10-8, DNA (Rattus norvegicus strain Wistar n-chimaerin cDNA plus flanks) 143561-16-4, DNA (Rattus norvegicus clone pF6 mitochondria photosynthetic coupling factor 6 cDNA plus flanks) 143910-47-8 144714-29-4, DNA (Rattus clone RPI/λ43 gene ARPP 21 cAMP-regulated phosphoprotein cDNA plus flanks) 145010-36-2, DNA (Rattus protein GRP78 (glucose-regulated protein 78) cDNA) 145464-10-4 145793-14-2 145886-43-7, DNA (Rattus norvegicus strain Sprague-Dawley proteoglycan glypican cDNA plus flanks) 146193-06-8, DNA (rat neuromedin U cDNA plus flanks) 146194-05-0, DNA (Rattus norvegicus gene mss4 protein Mss4 cDNA plus flanks) 146883-33-2, DNA (Rattus cytochrome

oxidase subunit I cDNA C-terminal fragment plus 3'-flank) 146888-64-4, DNA (Rattus phosphoprotein phosphatase isoenzyme 2C2 cDNA plus flanks) 147221-92-9, DNA (Rattus norvegicus gene FGFR-1 fibroblast growth factor receptor type 1 isoform β cDNA plus flanks) 147825-50-1, DNA (Rattus norvegicus clone p16a carnitine palmitoyltransferase isoenzyme I cDNA plus flanks) 147925-73-3 148167-97-9, DNA (Rattus norvegicus clone AT-3 fibroblast growth factor 7 cDNA plus 5'-flank) 148187-07-9, DNA (Rattus rattus strain Wistar clone lambda 6TRA8 glutathione transferase cDNA plus flanks) 148187-11-5, DNA (Rattus rattus clone L6 RNA polymerase II large subunit gene exon) 148282-71-7, DNA (Rattus transcription factor EF1 gene plus flanks) 148512-27-0, DNA (Rattus norvegicus strain BDIX clone DHD/K12/TRb gene Tage4 antigen pE4 cDNA plus flanks) 148984-46-7, DNA (Rattus norvegicus receptor SSR (signal sequence receptor) subunit γ cDNA plus flanks) 149215-12-3 149346-72-5, DNA (Rattus sp. gene β-ARK β-adrenergic receptor kinase (phosphorylating) cDNA plus 3'-flank) 149765-87-7, DNA (Rattus norvegicus strain Sprague-Dawley gene HSP70 heat-shock protein HSP70 cDNA plus flanks) 149799-70-2 150050-36-5 150219-95-7, DNA (Rattus norvegicus clone H35 gene CL-6 growth response protein cDNA plus flanks) 150421-46-8 150575-25-0, DNA (Rattus norvegicus strain Sprague-Dawley clone pUCcEH1 gene cEH epoxide hydratase cDNA plus flanks) 150754-92-0 151246-13-8 151279-36-6 151349-69-8 151526-32-8 151633-16-8 151715-43-4 151822-04-7, DNA (Rattus transcription factor repressor CREM isoform ICER cDNA plus flanks) 152053-29-7, DNA (Rattus norvegicus strain Sprague-Dawley gene BTG1 protein BTG1 C-terminal fragment-specifying plus 3'-flank) 152283-39-1, DNA (Rattus norvegicus strain Wistar clone rMax-S gene Max transcription factor Max cDNA) 152473-04-6, DNA (Rattus norvegicus strain Sprague-Dawley clone S20-E transcription factor CREM isoform CREMΔC-G cDNA plus flanks) 153320-83-3 153377-85-6, DNA (Rattus norvegicus strain Wistar mitochondria-associated gene RTP-β acetyl coenzyme A acyltransferase subunit β cDNA plus flanks) 153768-65-1, DNA (Rattus multicatalytic proteinase proteasome subunit RC10-II cDNA plus flanks) 154211-54-8 154298-83-6 154449-00-0, DNA (cDNA plus flanks) 154449-77-1 154946-36-8 154946-43-7, DNA (Rattus norvegicus gene LDH-B lactate dehydrogenase isozenzyme B cDNA plus flanks) 155120-31-3 155285-20-4, DNA (Rattus norvegicus strain Sprague-Dawley clone pRLTK transketolase cDNA plus flanks) 155610-50-7, DNA (Rattus norvegicus parathormone receptor gene exon T) 155712-56-4, DNA (Rattus norvegicus strain Noble gene c-Ki-ras Ras protein p21c-Ki-ras cDNA plus 3'-flank) 157115-04-3 157574-36-2 158126-95-5, DNA (Rattus norvegicus strain Sprague-Dawley ornithine decarboxylase-inhibiting protein cDNA plus flanks) 158682-55-4, DNA (Rattus norvegicus strain Sprague-Dawley phosphoprotein phosphatase isoenzyme T cDNA plus flanks) 158795-21-2 158929-76-1 159869-06-4, DNA (Rattus norvegicus clone Nb2 cyclin D2 cDNA plus flanks) 160102-90-9 160102-91-0, DNA (Rattus norvegicus clone ubc4a gene E217kB ubiquitin conjugating enzyme cDNA plus flanks) 160119-47-1 160340-30-7, DNA (Rattus prostanoid receptor type FP cDNA) 160898-62-4, DNA (Rattus clone 12 prostacyclin receptor cDNA plus flanks) 161274-17-5, DNA (Rattus norvegicus strain Sprague-Dawley clone λCKRα choline kinase gene exon 1 plus 5'-flank) 161573-42-8 162030-25-3, DNA (Rattus norvegicus strain Sprague-Dawley protein MIBP1 c-myc intron-binding protein 1) cDNA plus flanks) 163951-74-4 164373-82-4, DNA (Rattus norvegicus strain Sprague-Dawley annexin VI cDNA plus flanks) 164956-77-8, DNA (Rattus norvegicus strain Holtzman clone D920 intestinal epithelium proliferating cell transcript-associated cDNA) 165764-61-4, DNA (Rattus norvegicus strain Sprague-Dawley nucleic acid binding protein cDNA plus flanks) 166218-33-3, DNA (Rattus norvegicus strain Wistar clone DS112-36 carnitine palmitoyltransferase sequence

homolog cDNA plus flanks) 167248-08-0, DNA (Rattus norvegicus pyruvate carboxylase cDNA plus flanks) 167717-35-3, DNA (Rattus norvegicus clone TPCR06 gene tpcr06 olfactory receptor fragment-specifying cDNA) 168668-63-1, DNA (Rattus clone RPCAG66 EST (expressed sequence tag)) 168672-02-4 168672-96-6, DNA (Rattus clone RPCAW32 EST (expressed sequence tag)) 168673-62-9, DNA (Rattus clone RPCAY40 EST (expressed sequence tag)) 168719-92-4, DNA (Rattus clone RPNAS13 EST (expressed sequence tag)) 169073-73-8 169714-51-6, DNA (Rattus norvegicus gene γ-PAK protein kinase(phosphorylating) PAK2 cDNA plus flanks) 169714-84-5 169715-36-0, DNA (Rattus norvegicus strain Sprague-Dawley gene MEK5 gene MEK5 mitogen-activated protein kinase kinase isoenzyme MEK5α-1 cDNA plus flanks) 169717-57-1, DNA (Rattus norvegicus syntaxin binding protein Munc18-2 cDNA plus flanks) 169724-41-8 169729-58-2, DNA (Rattus norvegicus strain Sprague-Dawley clone R3A lactogen receptor cDNA plus flanks) 169730-20-5 170176-45-1, DNA (Rattus norvegicus strain Sprague-Dawley gene CYP1B1 cytochrome P 450 1B1 cDNA plus flanks) 170315-97-6 170335-02-1, DNA (Rattus norvegicus gene rab3c G protein (guanine nucleotide-binding protein) RAB3C fragment-specifying cDNA) 170610-53-4 172200-82-7, DNA (Rattus norvegicus protein kinase (phosphorylating) ROKα cDNA plus flanks) 172712-78-6, DNA (Rattus norvegicus strain Sprague-Dawley cholesterol esterase cDNA plus flanks) 172776-74-8 173333-49-8, DNA (Rattus norvegicus strain Sprague Dawley gene PPARδ peroxisome proliferator-activated receptor δ cDNA plus flanks) 173486-85-6 173708-20-8, DNA (Rattus norvegicus gene VH6 phosphoprotein (phosphotyrosine) phosphatase cDNA plus flanks) 173755-76-5 174053-72-6, DNA (Rattus norvegicus clone 36RbARP/10CorARP/5CerARP gene rARP atrophin-1 sequence homolog cDNA plus flanks)cDNA) 174129-15-8, GenBank x90823 174170-83-3 175112-29-5 175137-96-9 176193-92-3, DNA (Rattus norvegicus strain Sprague-Dawley gene RDJ1 molecular chaperone DnaJ sequence homolog cDNA plus flanks) 176893-38-2 177014-59-4, DNA (Rattus norvegicus strain Wistar gene POZF-1 zinc finger-containing protein cDNA plus flanks) 177303-36-5, DNA (Rattus norvegicus gene MEKK1 mitogen-activated protein kinase kinase kinase cDNA plus flanks) 177645-04-4, DNA (Rattus norvegicus dihydropyrimidinase cDNA plus flanks) 178148-46-4, DNA (Rattus norvegicus strain Sprague-Dawley gene M6P/IGF2r insulin-like growth factor II receptor cDNA plus flanks) 178409-93-3 179492-07-0, DNA (Rattus norvegicus centaurin α cDNA plus flanks) 179522-64-6, DNA (Rattus norvegicus strain Wistar clone pBACS II acyl coenzyme A synthetase isoenzyme 3 cDNA plus flanks) 179794-71-9, DNA (Rattus norvegicus strain Sprague-Dawley BRM (brahma) protein fragment-specifying cDNA) 179794-72-0, DNA (Rattus norvegicus strain Sprague-Dawley clone 68 gene hsp70.2 heat-shock protein HSP 70 C-terminal fragment specifying cDNA plus 3'-flank) 179972-35-1, DNA (Rattus norvegicus strain Sprague-Dawley hormone-sensitive lipase testicular isoenzyme cDNA plus flanks) 180171-78-2 180567-12-8 181013-93-4 182331-12-0, DNA (Rattus norvegicus gene Lot1 protein Lot1 cDNA plus flanks)) 182912-47-6 182983-57-9, DNA (Rattus norvegicus strain Wistar clone pCO100 EST (expressed sequence tag)) 182983-88-6, DNA (Rattus norvegicus strain Wistar clone pCO97 EST (expressed sequence tag)) 183192-22-5 183468-27-1, DNA (Rattus norvegicus strain Wistar-Kyoto clone Ssecks 322 3'-UTR fragment-specifying cDNA) 183641-21-6 183982-31-2 184385-27-1, DNA (Rattus norvegicus strain Wistar-Kyoto gene EGR1 sequence homolog protein N-terminal fragment specifying cDNA plus 5'-flank) 184695-59-8 184860-72-8 184864-37-7 184924-14-9, DNA (Rattus norvegicus clone gtB2 growth hormone receptor gene transcript 3'-UTR fragment-specifying cDNA) 185241-81-0 185570-55-2 185770-20-1 185774-15-6 186209-55-2, DNA (Rattus norvegicus strain Wister Imamichi phosphatidylinositol 4-kinase cDNA plus flanks) 186782-90-1, DNA (Rattus

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cDNA plus flanks) 195428-98-9 195432-79-2, DNA (Rattus norvegicus
strain Sprague-Dawley gene aiPLA2 peroxiredoxin 6 cDNA plus flanks)
195862-49-8, DNA (Rattus norvegicus strain Fischer F344 gene PP2A ARa
protein phosphoserine/phosphothreonine phosphatase 2A fragment-specifying
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subunit fragment-specifying cDNA) 195862-73-8
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL
(Biological study)
(nucleotide sequence; curcuminoids- and anthocyanins-responsive genes
in human adipocytes and their use in screenings of anti-obesity and
anti-diabetes drugs)

IT 231240-88-3 231241-24-0 231241-43-3 231241-62-6 231241-79-5
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norvegicus gene parathymosin α cDNA plus 3'-flank) 383835-68-5
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(Rattus rattus strain Fischer gene MC3-R pituitary hormone receptor
melanocortin receptor 3 cDNA plus flanks) 391770-48-2, DNA (Rattus gene
LAL lysosomal acid lipase cDNA plus flanks) 391775-75-0, DNA (Rattus
norvegicus strain Sprague Dawley [hydroxymethylglutaryl-CoA reductase
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392193-73-6
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(nucleotide sequence; curcuminoids- and anthocyanins-responsive genes in human adipocytes and their use in screenings of anti-obesity and anti-diabetes drugs)

OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

L156 ANSWER 12 OF 18 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2005:60754 HCAPLUS Full-text
Correction of: 2004:1036571
DOCUMENT NUMBER: 142:233342
Correction of: 142:16836
TITLE: Sequences of human schizophrenia related genes and use for diagnosis, prognosis and therapy
INVENTOR(S): Liew, Choong-Chin
PATENT ASSIGNEE(S): Chondrogene Limited, Can.
SOURCE: U.S. Pat. Appl. Publ., 156 pp., Cont.-in-part of U.S. Ser. No. 802,875.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 51
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
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PRIORITY APPLN. INFO.:			US 1999-115125P	P	19990106
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ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The present invention is directed to detection and measurement of gene transcripts and their equivalent nucleic acid products in blood. Specifically provided is anal. performed on a drop of blood for detecting, diagnosing and monitoring diseases using gene-specific and/or tissue-specific primers. The present invention also describes methods by which delineation of the sequence and/or quantitation of the expression levels of disease-specific genes allows for an immediate and accurate diagnostic/prognostic test for disease or to assess the effect of a particular treatment regimen. [This abstract record is one of 3 records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

IC ICM C12Q001-68

INCL 435006000

CC 1-11 (Pharmacology)
Section cross-reference(s): 3, 6, 7, 9, 13

IT Enzymes, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(DNA-recombining, P1 cre; sequences of human schizophrenia-related genes and use for diagnosis, prognosis and therapy)

IT Enzymes, biological studies
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); PRP (Properties); BIOL (Biological study); USES (Uses)
(DNA-recombining, cre, Bacteriophage P1; sequences of human schizophrenia-related genes and use for diagnosis, prognosis and therapy)

IT Proteins
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); PRP (Properties); BIOL (Biological study); USES (Uses)
(REC14, meiotic recombination; sequences of human schizophrenia-related genes and use for diagnosis, prognosis and therapy)

IT Mannose receptors
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); PRP (Properties); BIOL (Biological study); USES (Uses)
(mannose 6-phosphate, cation dependent; sequences of human schizophrenia-related genes and use for diagnosis, prognosis and therapy)

IT 384589-69-9, GenBank X69951 384591-36-0, DNA (human clone PMScDNA 2 cDNA) 384591-68-8 384591-94-0, DNA (human 4E-binding protein 2 cDNA) 384591-99-5 384593-14-0 384593-59-3 384593-85-5 384593-87-7, DNA (human cell line KG-1 cDNA) 384594-74-5 384597-53-9 384599-49-9 384602-52-2 384602-99-7 384603-26-3 384605-20-3 384608-61-1 384616-50-6 384619-95-8 384621-15-2 384626-08-8 384626-89-5 384626-98-6 384631-46-3, DNA (human cell line KG-1 cDNA) 384631-48-5, DNA (human cell line KG-1 cDNA) 384631-75-8, DNA (human cell line U937 cDNA) 384633-60-7 384635-17-0, DNA (human cell line Hela clone LAS34) 384636-34-4, DNA (human protein EB1 cDNA plus flanks) 384640-82-8 384645-36-7 384647-10-3 384648-62-8 384649-18-7, DNA (human gene hPMSR2) 384649-26-7, GenBank E12795 384649-28-9 384652-67-9, DNA (human gene Orc2 cDNA) 384653-64-9 384653-73-0, DNA (human PDGF associated protein cDNA) 384655-82-7 384657-73-2, DNA (human gene ANK3 cDNA) 384657-76-5 384657-95-8 384658-53-1 384659-13-6, GenBank E12457 384664-77-1 384674-62-8 384675-36-9 384675-48-3 384675-52-9 384676-63-5 384681-77-0 384683-28-7, DNA (human PRSM1 cDNA) 384683-72-1 384685-28-3, DNA (human clone 765b9 cDNA) 384685-34-1, DNA (human hTOM34p cDNA) 384692-81-3 384696-39-3 384696-51-9 384725-63-7 384726-11-8 384726-70-9, DNA (human aminopeptidase cDNA) 384727-47-3 384728-31-8 384729-18-4, DNA (human

gene SCA2 cDNA) 384737-67-1, DNA (human nel-related protein 2) 384746-08-1 384747-68-6 384747-76-6 384749-83-1, DNA (human gene Sec62 cDNA) 384750-18-9, DNA (human gene hTcf-4 cDNA) 384753-40-6 384754-28-3 384754-30-7, DNA (human WWP2 cDNA) 384754-40-9, DNA (human cell line Jurkat cDNA) 384763-37-5, DNA (human gene hsReq) 384765-62-2, DNA (human clone hg00111s1 cDNA) 384765-66-6, DNA (human clone HG0246 cDNA) 384765-69-9 384765-76-8 384770-08-5 384779-76-4 384779-84-4, DNA (human CASH alpha protein cDNA) 384780-01-2 384780-40-9, DNA (human gene IKK alpha cDNA) 384781-28-6 384781-62-8 384783-31-7 384970-88-1 384976-19-6, DNA (human acyloxyacyl hydrolase cDNA) 384976-48-1 384976-79-8, DNA (human clone pAH12 cDNA) 384977-53-1, DNA (human clone CPH-70) 384977-70-2 384978-99-8 384979-60-6, GenBank M97820 384983-79-3 384986-45-2 384998-64-5 385032-56-4 385038-39-1 385039-32-7 385039-64-5 385091-85-0, DNA (human cell line RAJI cDNA) 385096-20-8, DNA (human cell line IARC-EW11 cDNA) 385097-49-4, DNA (human TAFII32 precursor cDNA) 385098-08-8 385100-04-9 385102-04-5, DNA (human gene MLN 64 cDNA) 385105-58-8, DNA (human clone GT212) 385109-43-3 385134-88-3, DNA (human cell line HL60 cDNA) 385172-72-5 385191-00-4, GenBank E14353 385206-59-7, DNA (human gene NPIK-C cDNA) 385208-41-3 385209-26-7 385214-41-5, DNA (human clone B8 RanBPM cDNA) 385214-99-3, DNA (human gene HUMP68) 385215-03-2 385218-12-2 385220-73-5, DNA (human cell line HeLa SPOP cDNA) 385220-92-8 385222-09-3 385222-37-7, DNA (human gene sycl cDNA) 385225-89-8 385231-37-8 385231-40-3, DNA (human gene CYP-33 cDNA) 385243-62-9 385244-36-0 385245-66-9, DNA (human gene SBF1 cDNA) 385252-57-3 385252-59-5 385252-63-1 385271-98-7 385283-03-4 385283-09-0 385283-63-6, DNA (human E25 protein cDNA) 385283-71-6 385285-07-4, DNA (human gene DFF40 cDNA) 385287-63-8 385302-48-7 385310-49-6 385313-06-4, DNA (human gene IKAP cDNA) 385314-50-1, DNA (human gene TIRC7 cDNA) 385314-55-6 385321-42-6, DNA (human gene IPFK-2 cDNA) 385331-27-1 385334-64-5 385335-71-7 385352-84-1, DNA (human gene HRIHFB2122 cDNA) 385352-86-3, DNA (human gene HRIHFB2157 cDNA) 385682-42-8 385745-17-5, DNA (human clone R-336P14 gene Spast) 386119-45-5, DNA (human gene ABCA1 cDNA) 386139-01-1, DNA (human gene PIDD cDNA) 386173-77-9, DNA (human gene NUDT9 cDNA) 389176-63-0, DNA (human cell line A431 cDNA) 389179-80-0, DNA (human gene ACTA1 cDNA) 389180-05-6, DNA (human isolate patient S cDNA) 389180-15-8 389180-18-1, DNA (human gene LNHR) 389180-30-7 389180-36-3, DNA (human 18S rRNA gene plus 5'-flank) 389180-37-4, GenBank K03432 389180-38-5, GenBank M29063 389180-45-4, GenBank M20259 389180-83-0, DNA (human gene ALOX12 cDNA) 389181-01-5 389181-05-9 389181-29-7, DNA (human gene TB1 cDNA) 389181-39-9, DNA (human gene KIN27 cDNA) 389181-98-0 389182-09-6, DNA (human gene CTSB cDNA) 389182-14-3, GenBank M24070 389182-15-4, DNA (human deoxycytidine kinase cDNA) 389182-17-6, GenBank J03620 389182-18-7 389182-20-1, DNA (human gene ECGF1) 389182-32-5 389182-33-6 389182-46-1 389182-50-7, DNA (human gene IL6 protein cDNA) 389182-51-8 389182-63-2 389182-67-6 389182-68-7, GenBank M32110 389182-69-8, DNA (human pleckstrin cDNA plus flanks) 389182-73-4 389182-85-8, DNA (human gene PSAP cDNA) 389182-92-7, DNA (human gene TFRC cDNA) 389182-94-9 389183-38-4, DNA (human cell line U937 cDNA) 389183-42-0, DNA (human gene HPF2 cDNA) 389183-96-4 389184-03-6 389184-08-1 389184-58-1, DNA (human gene KRT8 cDNA) 389184-63-8 389184-79-6 389184-98-9 389185-23-3, DNA (human lysozyme cDNA plus flanks) 389185-27-7, DNA (human gene HLA-DRB1L cDNA) 389185-49-3 389185-54-0 389185-71-1, GenBank M30496 389186-21-4, DNA (human cell line GM3299; GM637 cDNA) 389186-23-6 389186-41-8 389186-46-3 389186-50-9, DNA (human alpha globin gene) 389186-73-6 389186-97-4 389187-25-1 389188-73-2 389188-76-5 389188-96-9 389189-08-6, DNA (human gene SPTAN1 cDNA) 389189-10-0, GenBank M33509 389189-24-6, DNA (human gene GAPD)

389189-25-7, DNA (human gene CTLA1) 389189-27-9 389189-61-1, GenBank M31013 389189-79-1 389189-81-5, DNA (human gene TGFB1 cDNA) 389190-91-4, DNA (human gene A1A plus flanks) 389191-00-8, DNA (human alpha-D-galactosidase A gene) 389191-24-6, DNA (human gene NCL) 389191-27-9 389191-55-3 389191-82-6 389192-47-6 389192-61-4, GenBank M34458 389193-51-5 389195-52-2, GenBank M97168 389196-47-8 389196-79-6, DNA (human gene RBPJK cDNA)
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(nucleotide sequence; sequences of human schizophrenia-related genes and use for diagnosis, prognosis and therapy)

L156 ANSWER 13 OF 18 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2003:389345 HCAPLUS Full-text
DOCUMENT NUMBER: 139:191138
TITLE: A biochemical and pharmacological comparison of enzyme replacement therapies for the glycolipid storage disorder Fabry disease
AUTHOR(S): Lee, Karen; Jin, Xiaoying; Zhang, Kate; Copertino, Lorraine; Andrews, Laura; Baker-Malcolm, Jennifer; Geagan, Laura; Qiu, Huawei; Seiger, Keirsten; Barngrover, Debra; McPherson, John M.; Edmunds, Tim
CORPORATE SOURCE: Cell and Protein Therapeutics, Genzyme Corporation, Framingham, MA, 01701-9322, USA
SOURCE: Glycobiology (2003), 13(4), 305-313
CODEN: GLYCE3; ISSN: 0959-6658
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Fabry disease is a lysosomal storage disease arising from deficiency of the enzyme α-galactosidase A. Two recombinant protein therapeutics, Fabrazyme (agalsidase beta) and Replagal (agalsidase alfa), have been approved in Europe as enzyme replacement therapies for Fabry disease. Both contain the same human enzyme, α-galactosidase A, but they are produced using different protein expression systems and have been approved for administration at different doses. To determine if there is recognizable biochem. basis for the different doses, we performed a comparison of the two drugs, focusing on factors that are likely to influence biol. activity and availability. The two drugs have similar glycosylation, both in the type and location of the oligosaccharide structures present. Differences in glycosylation were mainly limited to the levels of sialic acid and mannose-6-phosphate present, with Fabrazyme having a higher percentage of fully sialylated oligosaccharides and a higher level of phosphorylation. The higher levels of phosphorylated oligomannose residues correlated with increased binding to mannose-6-phosphate receptors and uptake into Fabry fibroblasts in vitro. Biodistribution studies in a mouse model of Fabry disease showed similar organ uptake. Likewise, antigenicity studies using antisera from Fabry patients demonstrated that both drugs were indistinguishable in terms of antibody cross-reactivity. Based on these studies and present knowledge regarding the influence of glycosylation on protein biodistribution and cellular uptake, the two protein prepns. appear to be functionally indistinguishable. Therefore, the data from these studies provide no rationale for the use of these proteins at different therapeutic doses.

CC 1-10 (Pharmacology)
Section cross-reference(s): 7, 14

IT Fabry disease
Heart
Human
Kidney
Liver

Lysosomal storage disease
  Phosphorylation, biological
Post-translational processing
Sialylation
Spleen
   (biochem. and pharmacol. comparison of enzyme replacement therapies for glycolipid storage disorder Fabry disease)

IT Sialic acids
   RL: BSU (Biological study, unclassified); BIOL (Biological study)
   (biochem. and pharmacol. comparison of enzyme replacement therapies for glycolipid storage disorder Fabry disease)

IT 104138-64-9, Fabrazyme
   RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
   (Replagal; biochem. and pharmacol. comparison of enzyme replacement therapies for glycolipid storage disorder Fabry disease)

IT 59-23-4, Galactose, biological studies 131-48-6, N-Acetylneuraminic acid 2438-80-4, Fucose 3458-28-4, Mannose 3672-15-9, Mannose-6-phosphate 7512-17-6, N-Acetylglucosamine
   RL: BSU (Biological study, unclassified); BIOL (Biological study)
   (biochem. and pharmacol. comparison of enzyme replacement therapies for glycolipid storage disorder Fabry disease)

IT 9025-35-8, α-Galactosidase A
   RL: BSU (Biological study, unclassified); BIOL (Biological study)
   (deficiency; biochem. and pharmacol. comparison of enzyme replacement therapies for glycolipid storage disorder Fabry disease)

OS.CITING REF COUNT: 64 THERE ARE 64 CAPLUS RECORDS THAT CITE THIS RECORD (64 CITINGS)

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L156 ANSWER 14 OF 18 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2001:208390 HCAPLUS Full-text
DOCUMENT NUMBER: 134:248843
TITLE: Use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases
INVENTOR(S): Canfield, William M.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001019955	A2	20010322	WO 2000-US21970	20000914
WO 2001019955	A3	20011004		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,

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        DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
        CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
    US 6534300          B1    20030318   US 2000-635872        20000810
    US 6537785          B1    20030325   US 2000-636077        20000810
    US 6642038          B1    20031104   US 2000-636060        20000810
    US 6770468          B1    20040803   US 2000-636596        20000810
    CA 2383217          A1    20010322   CA 2000-2383217       20000914
    AU 2000073303       A     20010417   AU 2000-73303         20000914
    AU 783224           B2    20051006
    BR 2000014514       A     20020723   BR 2000-14514         20000914
    EP 1224266          A2    20020724   EP 2000-961335        20000914
    EP 1224266          B1    20070912
       R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
          IE, SI, LT, LV, FI, RO, MK, CY, AL
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    AT 373086           T     20070915   AT 2000-961335        20000914
    US 20020025550      A1    20020228   US 2001-895072        20010702
    US 6861242          B2    20050301
    US 20020150981      A1    20021017   US 2001-986552        20011109
    US 6670165          B2    20031230
    MX 2002002901       A     20031014   MX 2002-2901          20020314
    US 20030148460      A1    20030807   US 2002-306686        20021129
    US 6828135          B2    20041207
    US 20050089869      A1    20050428   US 2003-657280        20030909
    US 7067127          B2    20060627
    US 20060073498      A1    20060406   US 2005-199233        20050809
    US 7371366          B2    20080513
    US 20080176285      A1    20080724   US 2008-38018         20080227
PRIORITY APPLN. INFO.:                   US 1999-153831P    P  19990914
                                         US 2000-635872     A1 20000810
                                         US 2000-636060     A3 20000810
                                         US 2000-636596     A3 20000810
                                         WO 2000-US21970    W  20000914
                                         US 2003-657280     A1 20030909
                                         US 2005-199233     A1 20050809
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
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AB The lysosomal targeting pathway enzymes GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase and uses in production of highly phosphorylated lysosomal hydrolases that can be used to treat lysosomal storage diseases, are disclosed. Generally, the nucleic acid mols. coding for the enzymes are incorporated into expression vectors that are used to transfect host cells that express the enzymes. The expressed enzymes are recovered using monoclonal antibodies capable of selectively binding to bovine GlcNAc-phosphotransferase and to bovine phosphodiester α-GlcNAcase. Lysosomal hydrolases having high mannose structures are treated with GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase resulting in the production of asparagine-linked oligosaccharides that are highly modified with mannose 6-phosphate ("M6P"). The treated hydrolase binds to M6P receptors on the cell membrane and is transported into the cell and delivered to the lysosome where it can perform its normal or a desired function. The highly phosphorylated lysosomal hydrolases are readily taken into the cell and into the lysosome during enzyme replacement therapy procedures.

IC ICM C12N

CC 7-8 (Enzymes)
Section cross-reference(s): 1, 12

ST GlcNAc phosphotransferase phosphodiester alpha GlcNAcase phosphorylation lysosomal hydrolase; lysosomal storage disease enzyme replacement therapy hydrolase

IT Disease, animal

(Aspartylglucosaminuria; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT Disease, animal
(Farber Lipogranulomatosis; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT Disease, animal
(Fucsidosis; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT Gangliosidosis
(GM1 gangliosidosis; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT Mucopolysaccharidosis
(Hunter's syndrome; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT Mucopolysaccharidosis
(Hurler's syndrome; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT Brain, disease
(Krabbe's disease; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT Mucopolysaccharidosis
(Maroteaux-Lamy syndrome; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT Disease, animal
(Morquio Syndrome; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT Disease, animal
(Mucolipidosis IV; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT Gangliosidosis
(Sandhoff's disease; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT Disease, animal
(Sanfilippo A; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT Disease, animal
(Schindler Disease; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT Disease, animal
(Sialidosis; use of GlcNAc-phosphotransferase and phosphodiester

α-GlcNAcase in production of highly phosphorylated
lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT Disease, animal
(Sly Syndrome; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT Gangliosidosis
(Tay-Sachs disease; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT Disease, animal
(Wolman's; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT Oligosaccharides, biological studies
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(asparagine-linked, in lysosomal hydrolase; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT Sialic acids
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(galactosialidosis; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT Brain, disease
(metachromatic leukodystrophy; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT Antibodies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(monoclonal; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT Phosphorylation, biological
(protein; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT Enzymes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(replacement therapy; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT Glycogen storage disease
(type II; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT Fabry disease
Gaucher disease
Genetic vectors
Hybridoma
Lysosomal storage disease
Lysosome

Molecular cloning
Niemann-Pick disease
Protein sequences
cDNA sequences
(use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT Antibodies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT Gangliosides
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT 9012-33-3
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(A; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT 9068-67-1, Sulfatase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Deficiency, Multiple; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT 9027-41-2, Hydrolase 9031-54-3, Sphingomyelinase
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(Lysosomal; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT 253334-78-0P, N-Acetylglucosamine-1-phosphodiester α-N-Acetylglucosaminidase (human)
RL: BPN (Biosynthetic preparation); CAT (Catalyst use); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amino acid sequence; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT 3458-28-4, Mannose
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(in lysosomal hydrolase; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT 9068-25-1, α-1,2-Mannosidase
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(inhibitor; use of GlcNAc-phosphotransferase and phosphodiester

α-GlcNAcase in production of highly phosphorylated
lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT 528-04-1
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(transfer of N-acetyl glucosamine-1-phosphate from;
use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT 28446-21-1, N-Acetyl glucosamine-1-phosphate
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(transfer of; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT 331288-42-7 331288-43-8, 2: PN: WO0119955 PAGE: 53 unclaimed DNA 331288-44-9, 3: PN: WO0119955 PAGE: 54 unclaimed DNA 331288-45-0, 4: PN: WO0119955 PAGE: 54 unclaimed DNA 331288-46-1 331288-47-2 331288-48-3 331288-49-4 331288-50-7 331288-51-8 331288-52-9 331288-53-0 331288-54-1, 16: PN: WO0119955 PAGE: 50 unclaimed DNA 331288-55-2 331288-56-3
RL: PRP (Properties)
(unclaimed nucleotide sequence; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT 331443-59-5 331443-60-8
RL: PRP (Properties)
(unclaimed protein sequence; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT 331434-83-4 331434-84-5 331434-86-7 331434-87-8 331434-89-0 331434-90-3 331434-91-4 331434-93-6 331434-95-8 331434-97-0 331434-99-2 331435-01-9 331435-02-0
RL: PRP (Properties)
(unclaimed sequence; use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT 75788-84-0P, E.C. 3.1.4.45 84012-69-1P, E.C. 2.7.8.17
RL: BPN (Biosynthetic preparation); CAT (Catalyst use); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation); USES (Uses)
(use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT 7512-17-6, N-Acetylglucosamine
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT 9001-42-7, α-Glucosidase 9001-45-0, β-Glucuronidase 9001-62-1 9001-67-6, Neuraminidase 9016-17-5, Arylsulfatase 9025-35-8, α-Galactosidase A 9025-62-1, Arylsulfatase C 9027-89-8, Galactocerebrosidase 9030-36-8, Galactose 6-sulfatase 9031-11-2 9037-65-4, α-Fucosidase

9068-68-2, Arylsulfatase A 9073-56-7, α-Iduronidase 9075-63-2, α-N-Acetyl galactosaminidase 9077-06-9, Heparan N-sulfatase 37228-64-1, Glucocerebroside β-Glucosidase 37288-40-7, N-Acetyl-α-glucosaminidase 37289-06-8, Acid Ceramidase 50936-59-9, Iduronate 2-sulfatase 55354-43-3, Arylsulfatase B 56467-83-5, Ceramidase 59299-00-2, N-Acetylgalactosamine-6-sulfatase 60320-99-2, N-Acetylglucosamine-6-sulfatase 79955-83-2, Acetyl CoA-α-glucosaminide N-acetyl transferase 83534-39-8, N-Glycosidase F

RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(use of GlcNAc-phosphotransferase and phosphodiester α -GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT 3672-15-9, Mannose 6-phosphate

RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)

(use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT 84444-90-6, Deoxymannojirimycin 109944-15-2, Kifunensine 149674-55-5, D-Mannoamidrazone 155501-85-2

RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)

(use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

OS.CITING REF COUNT: 12 THERE ARE 12 CAPLUS RECORDS THAT CITE THIS RECORD (30 CITINGS)

L156 ANSWER 15 OF 18 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1999:456601 HCAPLUS Full-text

DOCUMENT NUMBER: 131:209522

TITLE: The mannose 6-phosphate /insulin-like growth factor-II receptor is a substrate of type V transforming growth factor-β receptor

AUTHOR(S): Liu, Qianjin; Grubb, Jeffrey H.; Huang, Shuan Shian; Sly, William S.; Huang, Jung San

CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, St. Louis University School of Medicine, St. Louis, MO, 63104, USA

SOURCE: Journal of Biological Chemistry (1999), 274(28), 20002-20010

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The type V transforming growth factor β (TGF-β) receptor (TβR-V) is a ligand-stimulated acidotropic Ser-specific protein kinase that recognizes a motif of SXE/S(P)/D. This motif is present in the cytoplasmic domain of the mannose 6-phosphate/insulin-like growth factor-II (Man-6-P/IGF-II) receptor. The authors have explored the possibility that the Man-6-P/IGF-II receptor is a substrate of TβR-V. Purified bovine Man-6-P/IGF-II receptor was phosphorylated by purified bovine TβR-V in the presence of [γ-32P]ATP and MnCl2 with an apparent Km of 130 nM. TGF-β stimulated the phosphorylation of the Man-6-P/IGF-II receptor at 0° in mouse L cells overexpressing the Man-6-P/IGF-II

receptor and in wild-type mink lung epithelial (Mv1Lu cells) metabolically labeled with [32P]orthophosphate. The in vitro and in vivo phosphorylation of the Man-6-P/IGF-II receptor occurred at the putative phosphorylation sites as revealed by phosphopeptide mapping and amino acid sequence anal. TGF-β stimulated Man-6-P/IGF-II receptor-mediated uptake (.apprx.2-fold after 12 h treatment) of exogenous β-glucuronidase in Mv1Lu cells and type II TGF-β receptor (TβR-II)-defective mutant cells (DR26 cells) but not in type I TGF-β receptor (TβR-I)-defective mutant cells (R-1B cells) and human colorectal carcinoma cells (RII-37 cells) expressing TβR-I and TβR-II but lacking TβR-V. These results suggest the Man-6-P/IGF-II receptor serves as an in vitro and in vivo substrate of TβR-V and that both TβR-V and TβR-I may play a role in mediating the TGF-β-stimulated uptake of exogenous β-glucuronidase.

CC 2-10 (Mammalian Hormones)

IT Biological transport
(internalization, receptor; mannose 6-phosphate/IGF-II receptor as substrate of type V TGF-β receptor)

IT Biological transport
(intracellular, receptor; mannose 6-phosphate/IGF-II receptor as substrate of type V TGF-β receptor)

IT Lysosome
(mannose 6-phosphate/IGF-II receptor as substrate of type V TGF-β receptor)

IT Insulin-like growth factor II receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(mannose 6-phosphate/IGF-II receptor as substrate of type V TGF-β receptor)

IT Protein motifs
(phosphorylation site; mannose 6-phosphate/IGF-II receptor as substrate of type V TGF-β receptor)

IT Phosphorylation, biological
(receptor; mannose 6-phosphate /IGF-II receptor as substrate of type V TGF-β receptor)

IT Biological transport
(uptake, β-glucuronidase; mannose 6-phosphate/IGF-II receptor as substrate of type V TGF-β receptor)

IT Transforming growth factor receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(β-transforming growth factor type I; mannose 6 -phosphate/IGF-II receptor as substrate of type V TGF-β receptor)

IT Transforming growth factor receptors
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(β-transforming growth factor, type V; mannose 6 -phosphate/IGF-II receptor as substrate of type V TGF-β receptor)

IT Transforming growth factors
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(β1-; mannose 6-phosphate/IGF-II
receptor as substrate of type V TGF-β receptor)
IT 9012-33-3 9025-35-8, α-Galactosidase
9025-42-7, α-Mannosidase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(mannose 6-phosphate/IGF-II
receptor as substrate of type V TGF-β receptor)
IT 3672-15-9, Mannose 6-phosphate 67763-97-7,
Insulin-like growth factor-II
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(mannose 6-phosphate/IGF-II
receptor as substrate of type V TGF-β receptor)
IT 9001-45-0, β-Glucuronidase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(uptake; mannose 6-phosphate/IGF-II
receptor as substrate of type V TGF-β receptor)
OS.CITING REF COUNT: 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L156 ANSWER 16 OF 18 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 1995:632226 HCAPLUS Full-text
DOCUMENT NUMBER: 123:27238
ORIGINAL REFERENCE NO.: 123:4909a,4912a
TITLE: Cloning and expression of biologically active .alpha.-galactosidase A
INVENTOR(S): Desnick, Robert J.; Bishop, David F.; Ioannou, Yiannis A.
PATENT ASSIGNEE(S): The Mount Sinai School of Medicine of the City University of New York, USA
SOURCE: U.S., 73 pp. Cont.-in-part of U.S. Ser. No. 602,824. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5401650	A	19950328	US 1992-983451	19921130
US 5356804	A	19941018	US 1990-602824	19901024
US 5382524	A	19950117	US 1990-602608	19901024
EP 1375665	A1	20040102	EP 2003-11061	19911023
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
CA 2150555	A1	19940609	CA 1993-2150555	19931130
WO 9412628	A1	19940609	WO 1993-US11539	19931130
W: AU, BB, BG, BR, BY, CA, CZ, FI, HU, JP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, UZ				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9456817	A	19940622	AU 1994-56817	19931130
AU 691795	B2	19980528		
EP 670896	A1	19950913	EP 1994-902448	19931130
EP 670896	B1	20020206		
EP 670896	B2	20050427		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				

JP 08503615	T	19960423	JP 1994-513423	19931130
JP 4005629	B2	20071107		
EP 1020528	A2	20000719	EP 2000-200454	19931130
EP 1020528	A3	20001004		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
AT 213020	T	20020215	AT 1994-902448	19931130
ES 2168101	T3	20020601	ES 1994-902448	19931130
PT 670896	E	20020731	PT 1994-902448	19931130
EP 1942189	A2	20080709	EP 2007-22356	19931130
EP 1942189	A3	20080910		
EP 1942189	B1	20100414		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
AT 464386	T	20100415	AT 2007-22356	19931130
US 5580757	A	19961203	US 1994-261577	19940617
JP 2004121260	A	20040422	JP 2003-401467	20031201
JP 3598302	B2	20041208		

PRIORITY APPLN. INFO.:

US 1990-602608	A2	19901024
US 1990-602824	A2	19901024
EP 1991-920591	A3	19911023
US 1992-983451	A	19921130
EP 1994-902448	A3	19931130
EP 2000-200454	A3	19931130
JP 1994-513423	A3	19931130
WO 1993-US11539	W	19931130

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The present invention involves the production of large quantities of human α-Gal A by cloning and expressing the α-Gal A coding sequence in eukaryotic host cell expression systems. The eukaryotic expression systems, and in particular the mammalian host cell expression system described herein provide for the appropriate co-translational and post-translational modifications required for proper processing, e.g., glycosylation, phosphorylation, etc. And sorting of the expression product so that an active enzyme is produced. In addition, the expression of fusion proteins which simplify purification is described. Using the methods described herein, the recombinant α-Gal A is secreted by the engineered host cells so that it is recovered from the culture medium in good yield. The α-Gal A produced in accordance with the invention may be used, but is not limited to, in the treatment in Fabry Disease; for the hydrolysis of α-galactosyl residues in glycoconjugates; and/or for the conversion of the blood group B antigen on erythrocytes to the blood group O antigen.

IC ICM C12N009-40
ICS C12N009-10; C12N015-00

INCL 435208000

CC 3-2 (Biochemical Genetics)
Section cross-reference(s): 1, 7, 13, 15, 33

ST galactosidase alpha gene cloning human cell; Fabry disease treatment alpha galactosidase prodn; blood group antigen conversion alpha galactosidase; glycoconjugate galactosyl hydrolysis alpha galactosidase prodn

IT Eukaryote
Fabry's disease
Glycosidation
Lysosome
Mouse
Phosphorylation, biological
Protein sequences
Transformation, genetic
Virus, animal
(cloning and expression of biol. active α-

galactosidase A)

IT Animal cell
(mammalian; cloning and expression of biol. active α-galactosidase A)

IT Plasmid and Episome
(pST26; cloning and expression of biol. active α-galactosidase A)

IT Proteins, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(secretion; cloning and expression of biol. active α-galactosidase A)

IT Blood-group substances
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(B, cloning and expression of biol. active α-galactosidase A)

IT Animal cell line
(CHO, cloning and expression of biol. active α-galactosidase A)

IT Animal cell line
(COS-1, cloning and expression of biol. active α-galactosidase A)

IT Blood-group substances
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(O, cloning and expression of biol. active α-galactosidase A)

IT Biological transport
(absorption, cloning and expression of biol. active α-galactosidase A)

IT Reactors
(biocatalytic, cloning and expression of biol. active α-galactosidase A)

IT Deoxyribonucleic acid sequences
(complementary, cloning and expression of biol. active α-galactosidase A)

IT Carbohydrates and Sugars, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(conjugates, galactose-containing, cloning and expression of biol. active α-galactosidase A)

IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(mannose phosphate, cloning and expression of biol. active α-galactosidase A)

IT Genetic element
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(promoter, cloning and expression of biol. active α-galactosidase A)

IT Biological transport
(secretion, cloning and expression of biol. active α-galactosidase A)

IT 157817-60-2P 164059-42-1DP, fusion proteins with α-galactosidase A fragment

RL: BOC (Biological occurrence); BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); PROC (Process); USES (Uses)
(amino acid sequence of; cloning and expression of biol. active α-galactosidase A)

IT 9025-35-8P, α-Galactosidase A
RL: BOC (Biological occurrence); BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); PROC (Process); USES (Uses)
(cloning and expression of biol. active α-galactosidase A)

IT 9075-63-2, α-N-Acetylgalactosaminidase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cloning and expression of biol. active α-galactosidase A)

IT 9075-81-4, α2-6 Sialyltransferase
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(cloning and expression of biol. active α-galactosidase A)

IT 157817-58-8 164059-39-6 164059-40-9 164059-41-0D, fusion products with α-galactosidase cDNA fragment
RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(nucleotide sequence of; cloning and expression of biol. active α-galactosidase A)

IT 3672-15-9, Mannose 6-phosphate
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(receptors; cloning and expression of biol. active α-galactosidase A)

IT 9002-03-3, Dihydrofolate reductase
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(selectable marker; cloning and expression of biol. active α-galactosidase A)

IT 59-05-2, Methotrexate
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(selection; cloning and expression of biol. active α-galactosidase A)

OS.CITING REF COUNT: 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L156 ANSWER 17 OF 18 BIOTECHNO COPYRIGHT 2010 Elsevier Science B.V. on STN DUPLICATE
ACCESSION NUMBER: 1995:25212634 BIOTECHNO Full-text
TITLE: A method for monitoring the glycosylation of recombinant glycoproteins from conditioned medium, using fluorophore-assisted carbohydrate

electrophoresis
AUTHOR: Friedman Y.; Higgins E.A.
CORPORATE SOURCE: Genzyme Corporation, One Mountain Road,Framingham, MA 01701-9322, United States.
SOURCE: Analytical Biochemistry, (1995), 228/2 (221-225)
CODEN: ANBCA2 ISSN: 0003-2697
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
We have developed a method for monitoring the N-glycosylation of recombinant glycoproteins directly from conditioned medium samples. Proteins in the conditioned medium are separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and electroblotted onto polyvinylidene fluoride membranes. After staining the membranes with Coomassie blue, the protein(s) of interest is excised. Oligosaccharides are released from the membrane-bound glycoprotein by digesting with peptide N.sup.4-(acetyl-β- glucosaminyl) asparagine amidase and labeled with the fluorophore 8-aminonaphthalene-1,3,6-trisulfonate (ANTS). Labeled oligosaccharides are then separated on polyacrylamide gels which allow for the direct comparison of samples. We have shown that recombinant human lysosomal hydrolase . alpha.- galactosidase A is N-glycosylated with both sialylated and phosphorylated oligosaccharides. ANTS-labeled oligosaccharide bands from α-galactosidase A were isolated from polyacrylamide gels. Sialylated and phosphorylated bands were identified by shifts in their electrophoretic mobility after digesting with neuraminidase or alkaline phosphatase to remove sialic acid or phosphate groups, respectively. Using the ANTS-labeled oligosaccharides from α- galactosidase A, we have shown that polyacrylamide gels can be used to resolve sialylated and phosphorylated oligosaccharide structures.
CONTROLLED TERM: *glycoprotein; *oligosaccharide; *polyacrylamide gel; *recombinant protein; *protein glycosylation; article; carbohydrate analysis; controlled study; phosphorylation; polyacrylamide gel electrophoresis; priority journal; protein determination; sialylation

L156 ANSWER 18 OF 18 Elsevier Biobase COPYRIGHT 2010 Elsevier Science B.V. on STN DUPLICATE 1
ACCESSION NUMBER: 1998093557 ESBIOBASE Full-text
TITLE: Human α-galactosidase A: Characterization of the N-linked oligosaccharides on the intracellular and secreted glycoforms overexpressed by Chinese hamster ovary cells
AUTHOR(S): Matsuura, Fumito; Ohta, Masaya; Ioannou, Yiannis A.; Desnick, Robert J.
CORPORATE SOURCE: Matsuura, Fumito; Ohta, Masaya (Department of Biotechnology, Fukuyama University, Fukuyama, Hiroshima 729-02 (JP)); Ioannou, Yiannis A.; Desnick, Robert J. (Department of Human Genetics, Mount Sinai School of Medicine, Fifth Avenue and 100th Street, New York, NY 10029-6574 (US))

SOURCE: Glycobiology (Apr 1998) Volume 8, Number 4, pp. 329-339, 40 refs.
CODEN: GLYCE3 ISSN: 0959-6658
DOI: 10.1093/glycob/8.4.329
COUNTRY OF PUBLICATION: United Kingdom
DOCUMENT TYPE: Journal; Article
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 31 Jan 2009
Last updated on STN: 31 Jan 2009

ABSTRACT: Human α-galactosidase A (α-Gal A) is the lysosomal glycohydrolase that cleaves the terminal α-galactosyl moieties of various glycoconjugates. Overexpression of the enzyme in Chinese hamster ovary (CHO) cells results in high intracellular enzyme accumulation and the selective secretion of active enzyme. Structural analysis of the N-linked oligosaccharides of the intracellular and secreted glycoforms revealed that the secreted enzyme's oligosaccharides were remarkably heterogeneous, having high mannose (63%), complex (30%), and hybrid (5%) structures. The major high mannose oligosaccharides were Man 5-7 GlcNAc 2 species. Approximately 40% of the high mannose and 30% of the hybrid oligosaccharides had phosphate monoester groups. The complex oligosaccharides were mono-, bi-, 2,4-tri-, 2,6-tri- and tetraantennary with or without core-region fucose, many of which had incomplete outer chains. Approximately 30% of the complex oligosaccharides were mono- or disialylated. Sialic acids were mostly N-acetylneuraminic acid and occurred exclusively in α2,3-linkage. In contrast, the intracellular enzyme had only small amounts of complex chains (7.7%) and had predominantly high mannose oligosaccharides (92%), mostly Man 5 GlcNAc 2 and smaller species, of which only 3% were phosphorylated. The complex oligosaccharides were fucosylated and had the same antennary structures as the secreted enzyme. Although most had nature outer chains, none were sialylated. Thus, the overexpression of human α-Gal A in CHO cells resulted in different oligosaccharide structures on the secreted and intracellular glycoforms, the highly heterogeneous secreted forms presumably due to the high level expression and impaired glycosylation in the trans-Golgi network, and the predominately Man 5-7 GlcNAc 2 cellular glycoforms resulting from carbohydrate trimming in the lysosome. CLASSIFICATION CODE: 82.2.2 PROTEIN BIOCHEMISTRY, STRUCTURAL STUDIES, Amino Acid Sequences (Primary Structure); 82.2.8 PROTEIN BIOCHEMISTRY, STRUCTURAL STUDIES, Folding, Unfolding and Stability; 82.3.5 PROTEIN BIOCHEMISTRY, PROTEIN ENGINEERING, Expression Systems; 82.5.4 PROTEIN BIOCHEMISTRY, GENERAL ENZYMOLOGY, Mechanism; 82.8.6 PROTEIN BIOCHEMISTRY, HYDROLYTIC ENZYMES (EC 3.), Glycosylases and Glucosidases
SUPPLEMENTARY TERM: Chinese hamster ovary cell; Constitutive secretory pathway; Mannose-6-phosphate; N-linked oligosaccharide chain; Recombinant human α-galactosidase A
ORGANISM NAME: Animalia; Cricetinae; Cricetulus griseus

FILE 'HOME' ENTERED AT 11:08:26 ON 18 JUN 2010

SEARCH HISTORY

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=> d his nofile

     (FILE 'HOME' ENTERED AT 09:28:44 ON 18 JUN 2010)

     FILE 'CAPLUS' ENTERED AT 09:28:53 ON 18 JUN 2010
                E US2007-588425/APPS
L1            2 SEA SPE=ON  ABB=ON  US2007-588425/APPS
                D SCA
                E LYSOSOMAL STORAGE DISEASE+ALL/CT

     FILE 'REGISTRY' ENTERED AT 09:31:16 ON 18 JUN 2010
L2            1 SEA SPE=ON  ABB=ON  1174598-21-0
L3            1 SEA SPE=ON  ABB=ON  1174598-22-1
L4            1 SEA SPE=ON  ABB=ON  1174598-23-2
L5            1 SEA SPE=ON  ABB=ON  1174598-24-3
L6            1 SEA SPE=ON  ABB=ON  1174598-25-4
                D SCA L2
                D SCA L3
                D SCA L4
                D SCA L5
                D SCA L6
                E GALACTOSIDASE, A/CN
                E GALACTOSIDASE, A- (Z/CN
L7          189 SEA SPE=ON  ABB=ON  GALACTOSIDASE, A?/CN

     FILE 'HCAPLUS' ENTERED AT 09:34:21 ON 18 JUN 2010
L8            2 SEA SPE=ON  ABB=ON  US2007-588425/APPS
L9         4266 SEA SPE=ON  ABB=ON  L7
L10        3364 SEA SPE=ON  ABB=ON  GALACTOSIDASE/OBI(L)A/OBI
L11           9 SEA SPE=ON  ABB=ON  RHGAA/OBI OR RH GAA/OBI
L12           7 SEA SPE=ON  ABB=ON  GLUCOSE OXIDASE/OBI(L)A/OBI(L)ACID?/O
                BI
L13      212052 SEA SPE=ON  ABB=ON  RECOMB?/OBI
L14     1993781 SEA SPE=ON  ABB=ON  HUMAN/OBI
L15         105 SEA SPE=ON  ABB=ON  L9(L)L13
L16         141 SEA SPE=ON  ABB=ON  L10(L)L13
L17          34 SEA SPE=ON  ABB=ON  L10(L)L13(L)L14
L18          31 SEA SPE=ON  ABB=ON  GGA/OBI(L)(L13 OR L14)
L19        6247 SEA SPE=ON  ABB=ON  LYSOSOMAL STORAGE DISEASE+OLD,NT/CT
L20          36 SEA SPE=ON  ABB=ON  (L15 OR L16 OR L17 OR L18) AND L19
L21         325 SEA SPE=ON  ABB=ON  POMPE/OBI
                E POMPES
L22          20 SEA SPE=ON  ABB=ON  POMPES/OBI
                D SCA HITIND
L23           1 SEA SPE=ON  ABB=ON  (L15 OR L16 OR L17 OR L18) AND (L21 OR
                L22)
L24          21 SEA SPE=ON  ABB=ON  ZANKEL T?/AU
L25         189 SEA SPE=ON  ABB=ON  STARR C?/AU
L26          10 SEA SPE=ON  ABB=ON  L24 AND L25
L27           1 SEA SPE=ON  ABB=ON  (L24 OR L25 OR L1) AND (L15 OR L16 OR L17
                OR L18)
L28          15 SEA SPE=ON  ABB=ON  L8 OR ((L24 OR L25) AND (L15 OR L16 OR L17
                OR L18 OR L19 OR L21 OR L22))
L29           2 SEA SPE=ON  ABB=ON  L8 OR ((L24 OR L25) AND (L15 OR L16 OR L17
                OR L18))
L30        2691 SEA SPE=ON  ABB=ON  GALACTOSIDASE/OBI(A)A/OBI
L31          39 SEA SPE=ON  ABB=ON  L30(A)L13
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L32           20 SEA SPE=ON  ABB=ON  (L17 OR L18 OR L11 OR L12 OR L31) AND L19
L33           20 SEA SPE=ON  ABB=ON  (L17 OR L18 OR L11 OR L12 OR L31) AND L19
                AND L14
                D SCA L8
L34         1039 SEA SPE=ON  ABB=ON  RECEPTOR#/OBI(L)(MANNOSE 6 PHOSPHATE/OBI)

     FILE 'REGISTRY' ENTERED AT 09:46:28 ON 18 JUN 2010
L35            0 SEA SPE=ON  ABB=ON  SIALIC ACID/CN
                E SIALIC
                E ACETYLGLUCOSAMINE/CN
L36            1 SEA SPE=ON  ABB=ON  ACETYLGLUCOSAMINE/CN

     FILE 'HCAPLUS' ENTERED AT 09:47:05 ON 18 JUN 2010
L37         7785 SEA SPE=ON  ABB=ON  L36
L38        15302 SEA SPE=ON  ABB=ON  (ACETYL(W)GLUCOSAMINE OR ACETYLGLUCOSAMINE)
                /BI
                E SIALIC/BI
L39        23161 SEA SPE=ON  ABB=ON  (SIALIC ACID#)/BI

     FILE 'REGISTRY' ENTERED AT 09:48:08 ON 18 JUN 2010
L40            2 SEA SPE=ON  ABB=ON  GALACTOSE/CN

     FILE 'HCAPLUS' ENTERED AT 09:48:22 ON 18 JUN 2010
L41        29474 SEA SPE=ON  ABB=ON  L40
L42        64930 SEA SPE=ON  ABB=ON  GALACTOSE/BI
L43          132 SEA SPE=ON  ABB=ON  (L9 OR L10 OR L11 OR L12 OR L18) AND (L37
                OR L38)
L44           82 SEA SPE=ON  ABB=ON  (L9 OR L10 OR L11 OR L12 OR L18) AND L39
L45          811 SEA SPE=ON  ABB=ON  (L9 OR L10 OR L11 OR L12 OR L18) AND (L41
                OR L42)
L46           22 SEA SPE=ON  ABB=ON  L43 AND L44 AND L45
L47            0 SEA SPE=ON  ABB=ON  L43 AND L44 AND L45 AND L13
L48            8 SEA SPE=ON  ABB=ON  ((L43 AND (L44 OR L45)) OR (L44 AND L45))
                AND L13
                D SCA TI
L49       243556 SEA SPE=ON  ABB=ON  PHOSPHORYLAT?/BI
L50            3 SEA SPE=ON  ABB=ON  L46 AND L49
L51           20 SEA SPE=ON  ABB=ON  L34 AND (L9 OR L10 OR L11 OR L12 OR L18)
L52            6 SEA SPE=ON  ABB=ON  L51 AND (L49 OR L13)
                D SCA TI
L53            0 SEA SPE=ON  ABB=ON  L51 AND L46
L54            6 SEA SPE=ON  ABB=ON  L51 AND (L43 OR L44 OR L45)
L55            1 SEA SPE=ON  ABB=ON  L54 NOT L52
                D SCA

     FILE 'MEDLINE' ENTERED AT 09:53:26 ON 18 JUN 2010
L56           10 SEA SPE=ON  ABB=ON  ZANKEL T?/AU
L57          116 SEA SPE=ON  ABB=ON  STARR C?/AU
L58            2 SEA SPE=ON  ABB=ON  L56 AND L57
                D TRIAL 1-2
L59         3349 SEA SPE=ON  ABB=ON  ALPHA-GLUCOSIDASES/CT
L60           35 SEA SPE=ON  ABB=ON  RHGAA OR RH GAA
L61          821 SEA SPE=ON  ABB=ON  GLYCOGEN STORAGE DISEASE TYPE II/CT
L62        17870 SEA SPE=ON  ABB=ON  LYSOSOMAL STORAGE DISEASES+NT/CT
L63            0 SEA SPE=ON  ABB=ON  (L56 OR L57) AND (L60 OR (L59 AND L62))
L64            2 SEA SPE=ON  ABB=ON  (L58 OR L63)
L65           31 SEA SPE=ON  ABB=ON  L60 AND (L61 OR L62)
L66           31 SEA SPE=ON  ABB=ON  L60 AND L61
                D TRIAL 1-5
L67         9132 SEA SPE=ON  ABB=ON  PROTEIN ENGINEERING/CT
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L68      141392 SEA SPE=ON  ABB=ON  RECOMBINANT PROTEINS/CT
L69         438 SEA SPE=ON  ABB=ON  L59(L)GE/CT
L70          10 SEA SPE=ON  ABB=ON  L69 AND (L67 OR L68) AND L62
L71         114 SEA SPE=ON  ABB=ON  L69 AND (L67 OR L68 OR L59) AND L62
L72         113 SEA SPE=ON  ABB=ON  L69 AND L59 AND L61
L73           4 SEA SPE=ON  ABB=ON  L69 AND L60 AND L61
L74           4 SEA SPE=ON  ABB=ON  L69 AND L60 AND L62
L75        1573 SEA SPE=ON  ABB=ON  RECEPTOR, IGF TYPE 2/CT
L76       10510 SEA SPE=ON  ABB=ON  SIALIC ACIDS+NT/CT
L77       13419 SEA SPE=ON  ABB=ON  GALACTOSE/CT
L78        3482 SEA SPE=ON  ABB=ON  ACETYLGLUCOSAMINE/CT
L79           6 SEA SPE=ON  ABB=ON  L59 AND (L60 OR L67 OR L68) AND L75
L80           0 SEA SPE=ON  ABB=ON  L59 AND (L60 OR L67 OR L68) AND L76
L81           0 SEA SPE=ON  ABB=ON  L59 AND (L60 OR L67 OR L68) AND L77
L82           0 SEA SPE=ON  ABB=ON  L59 AND (L60 OR L67 OR L68) AND L78
L83       17338 SEA SPE=ON  ABB=ON  SIALIC ACID#
L84       28806 SEA SPE=ON  ABB=ON  GALACTOSE#
L85       10499 SEA SPE=ON  ABB=ON  ACETYL GLUCOSAMINE OR ACETYLGLUCOSAMINE
L86           0 SEA SPE=ON  ABB=ON  L59 AND (L60 OR L67 OR L68) AND LL83
L87           1 SEA SPE=ON  ABB=ON  L59 AND (L60 OR L67 OR L68) AND L83
L88           2 SEA SPE=ON  ABB=ON  L59 AND (L60 OR L67 OR L68) AND L84
L89           5 SEA SPE=ON  ABB=ON  L59 AND (L60 OR L67 OR L68) AND (L83 OR
                L84 OR L85)
L90           0 SEA SPE=ON  ABB=ON  (L56 OR L57) AND L69 AND (L67 OR L68 OR
                L60)

     FILE 'STNGUIDE' ENTERED AT 10:07:40 ON 18 JUN 2010

     FILE 'AGRICOLA, PASCAL, CABA, BIOTECHNO, WPIX, BIOSIS, DISSABS,
     ESBIOBASE, EMBASE, SCISEARCH' ENTERED AT 10:13:08 ON 18 JUN 2010
L91          60 SEA SPE=ON  ABB=ON  ZANKEL T?/AU
L92         797 SEA SPE=ON  ABB=ON  STARR C?/AU
L93       13980 SEA SPE=ON  ABB=ON  GALACTOSIDASE(A) A
L94         181 SEA SPE=ON  ABB=ON  RHGAA OR RH GAA
L95           0 SEA SPE=ON  ABB=ON  (GLUCOSE OXIDASE(A) A)(A) ACID?
L96     1588404 SEA SPE=ON  ABB=ON  RECOMB?
L97       10410 SEA SPE=ON  ABB=ON  LYSOSOM? STORAGE DISEASE#
L98       41383 SEA SPE=ON  ABB=ON  POMPE OR POMPES
L99        2204 SEA SPE=ON  ABB=ON  GLYCOGEN STORAGE DISEASE TYPE(W)(2 OR II)

L100       7817 SEA SPE=ON  ABB=ON  RECEPTOR#(2A)(MANNOSE 6 PHOSPHATE OR
                (INSULIN LIKE GROWTH FACTOR OR IGF)(A)(TYPE(W)(2 OR II)))
L101      64594 SEA SPE=ON  ABB=ON  SIALIC ACID#
L102      41248 SEA SPE=ON  ABB=ON  (ACETYL(W) GLUCOSAMINE OR ACETYLGLUCOSAMINE
                )/BI
L103     132565 SEA SPE=ON  ABB=ON  GALACTOSE
L104     933367 SEA SPE=ON  ABB=ON  PHOSPHORYLAT?
L105         33 SEA SPE=ON  ABB=ON  (GLUCOSE OXIDASE)(A) A
L106        646 SEA SPE=ON  ABB=ON  ASPARTYLGLUCOSAMINURIA
L107        479 SEA SPE=ON  ABB=ON  CHOLESTEROL ESTER STORAGE
L108       3878 SEA SPE=ON  ABB=ON  CYSTINOSIS
L109        187 SEA SPE=ON  ABB=ON  MANNOSIDASE DEFICIENCY
L110      12563 SEA SPE=ON  ABB=ON  MUCOPOLYSACCHARIDOS!S
L111       1301 SEA SPE=ON  ABB=ON  WOLMAN#
L112       1185 SEA SPE=ON  ABB=ON  FUCOSIDOS!S
L113       3225 SEA SPE=ON  ABB=ON  MUCOLIPIDOS!S
L114       1508 SEA SPE=ON  ABB=ON  SPHINGOLIPIDOS!S
L115      30549 SEA SPE=ON  ABB=ON  FABRY#
L116         52 SEA SPE=ON  ABB=ON  FARBER LIPOGRANULOMATOS!S
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L117      17226 SEA SPE=ON  ABB=ON  GAUCHER?
L118       9810 SEA SPE=ON  ABB=ON  NIEMANN PICK#
L119       2325 SEA SPE=ON  ABB=ON  (GLOBOID CELL#)(2A) LEUKODYSTROP?
L120         60 SEA SPE=ON  ABB=ON  SULFATIDOS!S
L121       6095 SEA SPE=ON  ABB=ON  GANGLIOSIDOS!S
L122       6139 SEA SPE=ON  ABB=ON  TAY SACHS
L123       2420 SEA SPE=ON  ABB=ON  SANDHOFF#
L124        682 SEA SPE=ON  ABB=ON  MULTIPLE SULFATASE DEFICIENC?
L125       4600 SEA SPE=ON  ABB=ON  METACHROMATIC(A) LEUKODYSTROPH?
L126          2 SEA SPE=ON  ABB=ON  (L91 OR L92) AND (L94 OR (L93 AND L96))
                AND (L97 OR L98 OR L99 OR L100 OR L101 OR L102 OR L103 OR L104
                OR L105 OR L106 OR L107 OR L108 OR L109 OR L110 OR L111 OR
                L112 OR L113 OR L114 OR L115 OR L116 OR L117 OR L118 OR L119
                OR L120 OR L121 OR L122 OR L123 OR L124 OR L125)
L127        177 SEA SPE=ON  ABB=ON  ((L93(5A) L96) OR L94) AND (L98 OR L99)
L128         61 SEA SPE=ON  ABB=ON  ((L93(5A) L96) OR L94 OR L105) AND (L97 OR
                L98 OR L99 OR L106 OR L107 OR L108 OR L109 OR L110 OR L111 OR
                L112 OR L113 OR L114 OR L115 OR L116 OR L117 OR L118 OR L119
                OR L120 OR L121 OR L122 OR L123 OR L124 OR L125) AND (L100 OR
                L101 OR L102 OR L103 OR L104)
L129          0 SEA SPE=ON  ABB=ON  L100 AND L102 AND L103 AND (L93 OR L94 OR
                L105)
L130          7 SEA SPE=ON  ABB=ON  ((L93(5A) L96) OR L94 OR L105) AND (L97 OR
                L98 OR L99 OR L106 OR L107 OR L108 OR L109 OR L110 OR L111 OR
                L112 OR L113 OR L114 OR L115 OR L116 OR L117 OR L118 OR L119
                OR L120 OR L121 OR L122 OR L123 OR L124 OR L125) AND L104
L131       8850 SEA SPE=ON  ABB=ON  (L100 AND (L102 OR L103)) OR (L102 AND
                L103)
L132          7 SEA SPE=ON  ABB=ON  ((L93(5A) L96) OR L94 OR L105) AND (L97 OR
                L98 OR L99 OR L106 OR L107 OR L108 OR L109 OR L110 OR L111 OR
                L112 OR L113 OR L114 OR L115 OR L116 OR L117 OR L118 OR L119
                OR L120 OR L121 OR L122 OR L123 OR L124 OR L125) AND L131
L133         12 SEA SPE=ON  ABB=ON  (L130 OR L132)
L134        202 SEA SPE=ON  ABB=ON  HUMAN(3A) L96(3A) L93

     FILE 'STNGUIDE' ENTERED AT 10:29:29 ON 18 JUN 2010

     FILE 'AGRICOLA, PASCAL, CABA, BIOTECHNO, WPIX, BIOSIS, DISSABS,
     ESBIOBASE, EMBASE, SCISEARCH' ENTERED AT 10:57:17 ON 18 JUN 2010
L135          1 SEA SPE=ON  ABB=ON  L134 AND (L98 OR L99)
L136        183 SEA SPE=ON  ABB=ON  L134 AND (L97 OR L98 OR L99 OR L106 OR
                L107 OR L108 OR L109 OR L110 OR L111 OR L112 OR L113 OR L114
                OR L115 OR L116 OR L117 OR L118 OR L119 OR L120 OR L121 OR
                L122 OR L123 OR L124 OR L125)
L137         14 SEA SPE=ON  ABB=ON  L104 AND ((L93(5A) L96) OR L94 OR L105)
L138         66 SEA SPE=ON  ABB=ON  L103 AND ((L93(5A) L96) OR L94 OR L105)
L139         44 SEA SPE=ON  ABB=ON  L100 AND ((L93(5A) L96) OR L94 OR L105)
L140         11 SEA SPE=ON  ABB=ON  ((L93(5A) L96) OR L94 OR L105) AND L101
L141          7 SEA SPE=ON  ABB=ON  ((L93(5A) L96) OR L94 OR L105) AND L102
L142         14 SEA SPE=ON  ABB=ON  L137 AND (L138 OR L139 OR L140 OR L141)
L143          7 SEA SPE=ON  ABB=ON  L138 AND (L139 OR L140 OR L141)
L144          3 SEA SPE=ON  ABB=ON  L139 AND (L140 OR L141)
L145          1 SEA SPE=ON  ABB=ON  L140 AND L141
L146         19 SEA SPE=ON  ABB=ON  (L142 OR L143 OR L144 OR L145)

     FILE 'STNGUIDE' ENTERED AT 11:01:17 ON 18 JUN 2010

     FILE 'AGRICOLA, PASCAL, CABA, BIOTECHNO, WPIX, BIOSIS, DISSABS,
     ESBIOBASE, EMBASE, SCISEARCH' ENTERED AT 11:02:14 ON 18 JUN 2010
                D QUE L126
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     FILE 'HCAPLUS' ENTERED AT 11:02:16 ON 18 JUN 2010
                D QUE L29

     FILE 'MEDLINE' ENTERED AT 11:02:17 ON 18 JUN 2010
                D QUE L64

     FILE 'MEDLINE, HCAPLUS, WPIX' ENTERED AT 11:02:18 ON 18 JUN 2010
L147          5 DUP REM L64 L29 L126 (1 DUPLICATE REMOVED)
                    ANSWERS '1-2' FROM FILE MEDLINE
                    ANSWERS '3-4' FROM FILE HCAPLUS
                    ANSWER '5' FROM FILE WPIX
                D IALL 1-2
                D IBIB AB HITIND 3-4
                D IFULL 5

     FILE 'STNGUIDE' ENTERED AT 11:02:47 ON 18 JUN 2010

     FILE 'AGRICOLA, PASCAL, CABA, BIOTECHNO, WPIX, BIOSIS, DISSABS,
     ESBIOBASE, EMBASE, SCISEARCH' ENTERED AT 11:04:29 ON 18 JUN 2010
                D QUE L130
                D QUE L132
                D QUE L135
L148         13 SEA SPE=ON  ABB=ON  (L130 OR L132 OR L135)
L149         12 SEA SPE=ON  ABB=ON  L148 NOT L126

     FILE 'HCAPLUS' ENTERED AT 11:04:34 ON 18 JUN 2010
                E LYSOSOMAL STORAGE DISEASES+ALL/CT
                D QUE L23
                D QUE L33
L150         19 SEA SPE=ON  ABB=ON  (L23 OR L33) NOT L29

     FILE 'MEDLINE' ENTERED AT 11:04:36 ON 18 JUN 2010
                D QUE L70
                D QUE L74
L151         12 SEA SPE=ON  ABB=ON  (L70 OR L74) NOT L64

     FILE 'STNGUIDE' ENTERED AT 11:04:55 ON 18 JUN 2010

     FILE 'MEDLINE, HCAPLUS, BIOTECHNO, WPIX, BIOSIS, DISSABS, ESBIOBASE,
     EMBASE, SCISEARCH' ENTERED AT 11:05:06 ON 18 JUN 2010
L152         37 DUP REM L151 L150 L149 (6 DUPLICATES REMOVED)
                    ANSWERS '1-12' FROM FILE MEDLINE
                    ANSWERS '13-31' FROM FILE HCAPLUS
                    ANSWERS '32-33' FROM FILE BIOTECHNO
                    ANSWERS '34-36' FROM FILE WPIX
                    ANSWER '37' FROM FILE DISSABS
                D IALL 1-12
                D IBIB AB HITIND 13-31
                D IALL 32-33
                D IFULL 34-36
                D IALL 37

     FILE 'STNGUIDE' ENTERED AT 11:05:48 ON 18 JUN 2010

     FILE 'AGRICOLA, PASCAL, CABA, BIOTECHNO, WPIX, BIOSIS, DISSABS,
     ESBIOBASE, EMBASE, SCISEARCH' ENTERED AT 11:07:13 ON 18 JUN 2010
                D QUE L129
                D QUE L146
L153          7 SEA SPE=ON  ABB=ON  L146 NOT (L126 OR L130 OR L132 OR L135)
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     FILE 'HCAPLUS' ENTERED AT 11:07:17 ON 18 JUN 2010
                D QUE L50
                D QUE L52
L154          8 SEA SPE=ON  ABB=ON  (L50 OR L52) NOT (L29 OR L23 OR L33)

     FILE 'MEDLINE' ENTERED AT 11:07:18 ON 18 JUN 2010
                D QUE L79
                D QUE L89
L155          8 SEA SPE=ON  ABB=ON  (L79 OR L89) NOT (L70 OR L74 OR L64)

     FILE 'STNGUIDE' ENTERED AT 11:07:49 ON 18 JUN 2010

     FILE 'MEDLINE, HCAPLUS, BIOTECHNO, BIOSIS, ESBIOBASE, EMBASE, SCISEARCH'
     ENTERED AT 11:08:05 ON 18 JUN 2010
L156         18 DUP REM L155 L154 L153 (5 DUPLICATES REMOVED)
                     ANSWERS '1-8' FROM FILE MEDLINE
                     ANSWERS '9-16' FROM FILE HCAPLUS
                     ANSWER '17' FROM FILE BIOTECHNO
                     ANSWER '18' FROM FILE ESBIOBASE
                D IALL 1-8
                D IBIB AB HITIND 9-16
                D IALL 17-18

     FILE 'HOME' ENTERED AT 11:08:26 ON 18 JUN 2010

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